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(71) Applicant *(for all designated States except US)*: RORER INTERNATIONAL (HOLDINGS), INC. [US/US]; 40 Cape Henlopen Drive, Lewes, DE 19958 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)* : MOLINO, Bruce, F. [US/US]; 2825 North Ford Drive, Hatfield, PA 19440 (US). DARKES, Paul, R. [US/US]; 1808 Braeburn Terrace, Landsdale, PA (US). EWING, William, R. [US/US]; 2304 Bradenburg Way, King of Prussia, PA 19406 (US).

(74) Agents: DARKES, Paul, R.; Rhône-Poulenc Rorer Inc., 500 Virginia Drive, #3A, Fort Washington, PA 19034 (US) et al.

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(54) Title: TETRAHYDROPYRIDOINDOLES AS CHOLECYSTOKININ AND GASTRIN ANTAGONISTS

(57) Abstract

This invention relates to tetrahydropyridoindoles, and analogues and derivatives thereof, to pharmaceutical compositions including such compounds, and to methods of treatment of cholecystokinin and gastrin-related disorders comprising the administration to a human or other animal in need of such therapy of a therapeutically effective amount of said compounds or compositions.

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TETRAHYDROPYRIDOINDOLES AS CHOLECYSTOKININ AND GASTRIN ANTAGONISTS

This application is a continuation-in-part application of U.S. application serial number 07/573,514, filed August 24, 1990, which in turn is a continuation-in-part application of U.S. application serial number 07/542,495 filed on June 21, 1990.

BACKGROUND OF INVENTION

1. Field of the Invention

This invention relates to certain compounds which antagonize the actions of the neuropeptides cholecystokinin (hereinafter CCK) and gastrin.

CCK and gastrin are peptides, endogenous in human and other species, which regulate biological functions in tissues in the GI tract and central nervous system (CNS). Gastrin and CCK regulate biological activity by acting as autocrine, parocrine, endocrine or neurocrine agents.

The first and principal form of gastrin isolated was the 17 amino acid residue peptide, G-17 or little gastrin. The second major molecular form of gastrin is the 34 amino acid residue peptide, G-34 or big gastrin. G-34 is considered the proform of G-17, but both forms of gastrin are biologically active and nearly equipotent. The smallest residue possessing full biological activity is G-4 which is the final 4 amino acids at the carboxy terminal. Sulfation of the tyrosine residue (6-amino acids from the C-terminal) is not necessary for expression of the bioactivity of gastrin and its congeners.

The major physiologic action of gastrin is the stimulation of acid secretion from the stomach. Gastrin stimulates acid secretion by at least three separate actions: direct stimulation of parietal cell activity; potentiating the actions of histamine, a paracrine stimulus; and by direct release of histamine.

Gastrin is a trophic hormone for gastric, fundic and intestinal mucosa and for the pancreas. Gastrin directly stimulates those biochemical processes, DNA and RNA synthesis, that are involved in tissue growth.

Gastrin also stimulates pepsin secretion and increases gastric mucosal blood flow. It causes electrolyte and water secretion by the stomach, pancreas, liver, and Brunner's glands.

Other possible actions of gastrin may involve the regulation of lower esophageal sphincter contraction and other smooth muscle contractions (motility) in the GI tract.

CCK is a linear amino acid polypeptide that occurs in several bioactive forms which have been reported. All of the [illegible] of the tyrosine residue at position 7, counting from the C-terminal, for the full expression of their biologic activity.

The principal physiologic actions of CCK are stimulation of gallbladder contraction and of pancreatic enzyme secretion. There is evidence which supports a physiologic role of CCK in the inhibition of gastric emptying, stimulation of pancreatic growth and release of pancreatic polypeptide.

Other possible actions of CCK include stimulation of insulin, glucagon, somatostatin and peptide YY release, stimulation of hepatic bile flow, intestinal motility, blood flow in the superior mesenteric artery, secretion of pepsinogen from gastric glands, and secretion of bicarbonate from the stomach and duodenum. In contrast to gastrin, CCK relaxes the lower esophageal sphincter.

In the nervous system CCK may act as a neurotransmitter or as a neuromodulator. As such, exogenous CCK has been shown to affect memory. Also levels of acetylcholine and dopamine have been affected by exogenous CCK. CCK has been implicated as well for producing the satiety effect, however, it is not clear if this is regulated by peripheral or central mechanisms.

There is considerable overlap in the biological activities elicited by gastrin and CCK. Therefore, gastrin receptor antagonists may also possess activity at the CCK receptors or vice versa.

2. Reported Developments

Four distinct chemical classes of CCK-A (peripheral CCK) receptor antagonists have been reported (see R.M. Freidinger, *Medicinal Research Reviews*, **9** (3), 271-290 (1989)).

(1) Cyclic nucleotides, e.g. dibutyryl cyclic GMP (see N. Boilos et al., *Am. J. Physiol.* **242**, G 161 (1982) and P. Robberecht et al., *Mol. Pharmacol.*, **17**, 268 (1982)).

(2) Amino acid derivatives, characterized by proglumide, a derivative of glutamic acid and N-acylated tryptophans, i.e. para-chlorobenzoyl-L-tryptophan (benzotript) (see W.F. Hahne et al., *Proc. Natl. Acad. Sci. USA*, **78**: 6304 (1981) and R.T. Jensen et al., *Biochem. Biophys. Acta.* **76**, 269 (1983)); also second generation proglumide analogues typified by Lorglumide and Loxiglumide (F. Makovec et al., *Arzneim-Forsch.*, **37**(II), 1265 (1987)). The latter two analogues have considerably better receptor affinity and selectivity.

(3) Peptide and pseudopeptide analogs based on the C-terminal end of CCK, especially analogues of CCK-8, Asp-Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-Phe-NH_2. Some examples are Cbz-Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-NH_2 (M. Spanarkel et al., *J. Biol. Chem.* **258**, 6746 (1983)) and Boc-Tyr(SO_3H)-Met-Gly-D-Trp-Nle-Asp-OCH_2CH_2Ph (M.F. Lignon et al. *J. Biol. Chem.* **262**, 7226 (1987)).

(4) Non-peptide structures,e.g. the fermentation product asperlicin (R.S.L. Chang et al., *Science* **230**, 177 (1985)). Subsequent medicinal chemistry done on this compound culminated in the 1,4-benzodiazepine (MK329) series having very high CCK-A affinity (B.E. Evans et al., *J. Med. Chem.* **31**, 2235-2246 (1988)).

Structurally related compounds which retain nanomolar level potency for the CCK-A receptor have recently been reported, e.g. 3-aminobenzolactam (R.S.L. Chang and W.H. Parsons, Eur. Pat. Appl. EP 166,345 (1986), and W.H. Parsons et al., *J. Med. Chem.*, **32**, 1681-1685 (1989) and ß-carbolines (B.E. Evans, Eur. Pat. Appl. EP 304,233 (1988) and M. Itonaga et al., *Japan. J. Pharmacol.*, **46**, 319-324 (1988)).

Compounds selective for the peripheral gastrin receptor also possess strong affinity for the CCK-B receptor (a CCK receptor located in the CNS). Presently there are no known agents which differentiate substantially between the CCK-B receptor and the peripheral gastrin receptor. Compounds selective for gastrin generally fall into two major classes.

(1) Peptide and pseudopeptide analogs based on C-terminal amino acids of CCK or gastrin, especially CCK-4 (Trp-Met-Asp-Phe-NH_2). Some examples are the pseudopeptide Boc-Trp-Leu-$\Psi(CH_2NH)$-Asp-Phe-NH_2 in which the amide bond between aspartic acid has been replaced by NH_2 but has no agonist activity (J. Martinez et al., *J. Med. Chem.*, **28**, 1874, (1985)).

Other analogues of CCK-4 containing partial retro-inverso modifications have been demonstrated to bind strongly to the gastrin receptor and block the effects of gastrin in the rat (in vivo) e.g. Boc-Trp-Leu-gAsp-m(R,S)Phe-NH_2 (M. Rodriguez et al., *J. Med. Chem.*, **30**, 758-763, (1987)).

Recently some cyclic cholecystokinin analogues of CCK-8 (Asp-Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-Phe-NH_2) e.g.

Boc-D-Asp-Tyr-($S0_3H$)-Ahx-D-Lys-Trp-Ahx-Asp-Phe-NH_2

(where Ahx = 2-aminohexanoic acid) have demonstrated selectivity for the CCK-B (CNS) receptor relative to CCK-A (peripheral), B. Charpentier, et al., *Proc. Natl. Acad. Sci. USA*, **85**, 1968-1972, (1988).

(2) Benzodiazepines. The 3-substituted 1,4-benzodiazepines effective as selective antagonists of CCK-A have been modified synthetically resulting in agents selective for the peripheral gastrin and CCK-B (brain) receptors, such as the Merck compound L-365,260 (V.J. Lotti and R.S.L. Chang, *Eur. J. of Pharm.*, **162**, 273-280 (1989), also M.G. Bock et al., *J. Med. Chem.*, **32**, 16-23, (1989)).

Other non-peptide, non-benzodiazepine compounds (e.g. analogs of Virginiamycin M1) have been reported to display strong binding affinity and

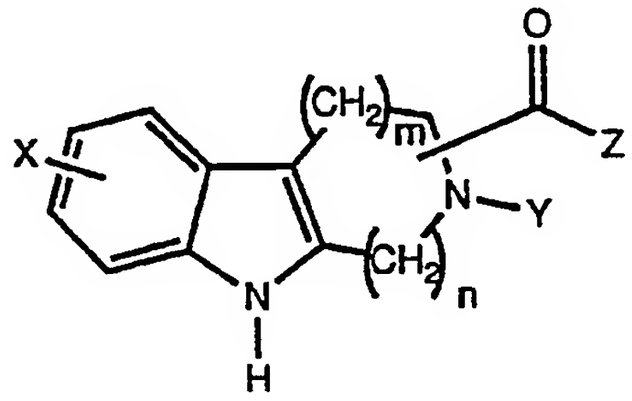
selectively for gastrin (relative to CCK-A) (Y.-K.T. Lam et al., U.S. Patent No. 4,762,923 (1988)).

Tetrahydropyridoindoles are reported to be active as gastrin and cholecystokinin antagonists in pending United States application serial no. 07/542,495, attorney docket no. A0135, filed on June 21, 1990, and United States Application Serial No.: 07/573,514, attorney Docket No.: A0135A, filed August 24, 1990, assigned to the same assignee as the present invention. N-arylcarbamoyl proline analogues are reported to be useful as cholecystokinin and gastrin antagonists in pending United States Application Serial No.: 07/697,177, filed May 8, 1991, assigned to the same assignee as the present invention.

The present invention relates to tetrahydropyridoindoles, and analogues and derivatives thereof, which are useful as cholecystokinin and gastrin antagonists.

SUMMARY OF THE INVENTION

Compounds of the present invention are described by Formula I

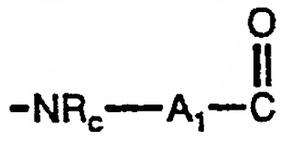


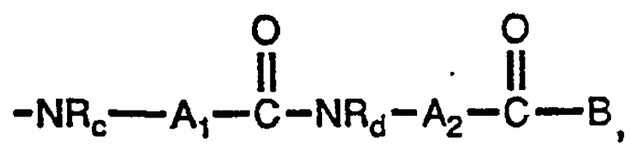
wherein:

X is an aryl group substituent;

Y is hydrogen, alkyl, substituted or unsubstituted aralkyl, acyl, substituted or unsubstituted aroyl, substituted or unsubstituted heterocyclylcarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl where the alkyl groups may be the same or different, substituted or unsubstituted arylcarbamoyl, substituted or unsubstituted N-alkyl arylcarbamoyl, alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, or substituted or unsubstituted aralkoxycarbonyl;

Z is substituted or unsubstituted nitrogen-containing heterocyclyl, $-NR_aR_b$ where R_a and R_b are independently hydrogen, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted diarylalkyl, or, when taken together, R_a and R_b may form $-(CH_2)_t-$ where t is 3, 4, or 5, or Z is



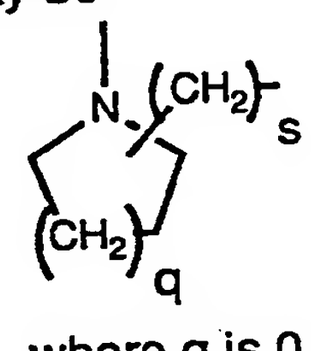


where

A_1 and A_2 are independently alkylene, substituted or unsubstituted phenylene, cycloalkylene, arylalkylene, arylalkylalkylene,

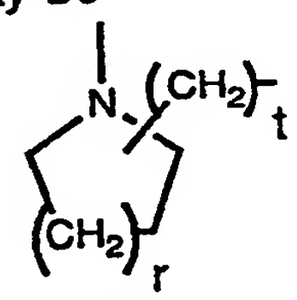
alkoxycarbonylalkylalkylene, aryloxycarbonylalkylalkylene, aralkoxycarbonylalkylalkylene, carboxyalkylalkylene, carbamoylalkylalkylene, alkylthioalkylalkylene, hydroxymethylmethylene, alkoxyalkylalkylene, aralkoxyalkylalkylene, aralkoxyalkylene, (1-hydroxyethyl)methylene, (4-hydroxyphenyl)methylmethylene, indol-3-ylmethylmethylene, imidazol-4-ylmethylmethylene, guanidinoalkylalkylene, or aminoalkylalkylene,

$-NR_c-A_1-$ may be



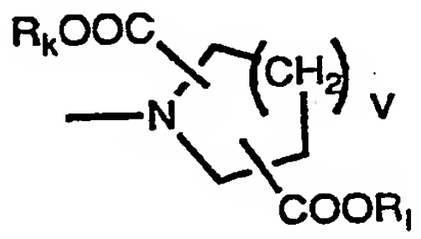
where q is 0, 1, 2, or 3, and
s is 0, 1, or 2; and

$-NR_d-A_2-$ may be



where r is 0, 1, 2, or 3, and
t is 0, 1, or 2;

B is hydroxy, alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted aryloxy or $-NR_fR_g$ where R_f and R_g are independently hydrogen, alkyl, substituted or unsubstituted aralkyl, carboxyalkyl, alkoxycarbonylalkyl, substituted or unsubstituted aryloxycarbonylalkyl or substituted or unsubstituted aralkoxycarbonylalkyl, or, when taken together, R_f and R_g may form $-(CH_2)_u-$ where u is 3, 4, or 5, or B is



where R_k and R_l are independently hydrogen, alkyl, or substituted or unsubstituted aralkyl,
and v is 0, 1, or 2;

R_c and R_d are independently hydrogen, alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted aralkyl;

m is 0, 1, 2, or 3; and

n is 0, 1, 2, 3, or 4;

or pharmaceutically acceptable salts thereof.

Additionally, this invention relates to pharmaceutical compositions

gastrointestinal, central nervous and appetite-controlling systems, such as irritable bowel syndrome, hypergastrinemia, excess pancreatic or gastric secretions, gastrointestinal ulcers, motility and neuroleptic disorders, Parkinson's disease, pain, malignancies of the lower esophagus, stomach, intestines and colon, comprising the administration to a human or other animal patient in need of such therapy of a compound or pharmaceutical composition described herein.

DETAILED DESCRIPTION OF THE INVENTION

As used above, and throughout the description of this invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Alkyl" means a saturated aliphatic hydrocarbon group which may be straight or branched and having about 1 to about 20 carbon atoms in the chain, or which may be cyclic or bicyclic. Branched means that a lower alkyl group such as methyl, ethyl or propyl is attached to a linear alkyl chain. Preferred straight or branched alkyl groups are the "lower alkyl" groups which are those alkyl groups having from 1 to about 6 carbons. Preferred cyclic or bicyclic alkyl groups include cyclohexyl and adamantyl.

"Aryl" means phenyl or naphthyl or phenyl or naphthyl substituted with one or more aryl group substituents which may be the same or different, where "aryl group substituent" includes alkyl, alkenyl, alkynyl, aryl, aralkyl, hydroxy, alkoxy, aryloxy, aralkoxy, hydroxyalkyl, acyl, formyl, carboxy, alkenoyl, aroyl, halo, nitro, trihalomethyl, cyano, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, acylamino, aroylamino, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, arylcarbamoyl, aralkylcarbamoyl, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, aralkylsulfonyl, aralkylsulfinyl, or -NRR' where R and R' are independently hydrogen, alkyl, aryl, or aralkyl.

"Analogue" means a compound which comprises a chemically modified form of a specific compound or class thereof, and which maintains the pharmaceutical and/or pharmacological activities characteristic of said compound or class.

"Derivative" means a chemically modified compound wherein the modification is considered routine by the ordinary skilled chemist, such as an ester or an amide of an acid, protecting groups, such as a benzyl group for an alcohol or thiol, and tert-butoxycarbonyl group for an amine.

"Aralkyl" means an alkyl group substituted by an aryl radical. Exemplary aralkyl groups include benzyl and phenethyl.

"Alkoxy" means an alkyl-O- group. Lower alkoxy groups are preferred. Exemplary groups include methoxy, ethoxy, n-propoxy, i-propoxy and n-butoxy.

"Aryloxy" means an aryl-O- group. Exemplary groups include phenoxy and 2-naphthyloxy.

"Aralkoxy" means an aralkyl-O- group. Exemplary groups include benzyloxy and phenethyloxy.

"Alkylene" means a straight or branched bivalent hydrocarbon chain the lower alkylene groups having from 1 to about 6 carbon atoms. Exemplary groups include methylene and ethylene.

"Phenylene" means a 1,2-, 1,3- or 1,4- bivalent phenyl group which may be unsubstituted or substituted with one or more aryl group substituents.

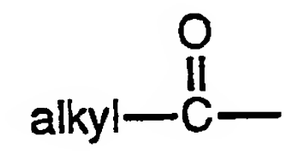
"Cycloalkylene" means a bivalent, saturated carbocyclic group having about 4 to about 8 carbon atoms. Preferred cycloalkylene groups include 1,2-, 1,3-, or 1,4- cis or trans-cyclohexanylene, and 1,1-cyclopentanylene.

"Aralkylalkylene" means an alkylene group substituted with an aryl group.

"Alkylalkylene" means an alkylene group substituted with an alkyl group. Preferred groups include methylmethylene and i-propylmethylene.

"Alkenyl" means an alkyl group containing a carbon-carbon double bond. Exemplary groups include allyl and vinyl.

"Alkynyl" means an alkyl group containing a carbon-carbon triple bond. Exemplary groups include ethynyl and propargyl.

"Acyl" means an  group. Preferred acyl groups are those in which the alkyl group is lower alkyl.

"Aroyl" means an aryl—C(=O)— group. Exemplary groups include benzoyl and 1- and 2-naphthoyl.

"Alkenoyl" means an alkenyl—C(=O)— group.

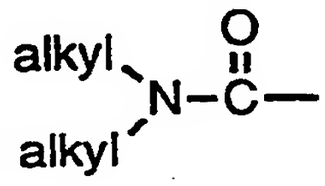
"Alkoxycarbonyl" means an alkyl-O—C(=O)— group. Preferred groups include methoxycarbonyl and ethoxycarbonyl.

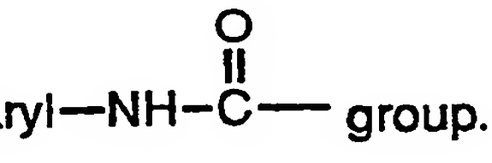
"Aralkoxycarbonyl" means an aralkyl-O—C(=O)— group. A preferred group is benzyloxycarbonyl.

"Aryloxycarbonyl" means an aryl-O—C(=O)— group. A preferred group is phenoxycarbonyl.

"Carbamoyl" is an NH_2C(=O)— group.

"Alkylcarbamoyl" is an alkyl—NH-C(=O)— group.

"Dialkyl carbamoyl is an  group where the alkyl groups may be the same or different.

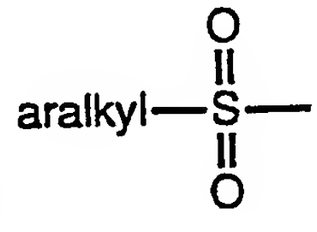
"Arylcarbamoyl" is an  group.

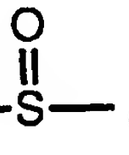
"Acylamino" is an acyl-NH- group.

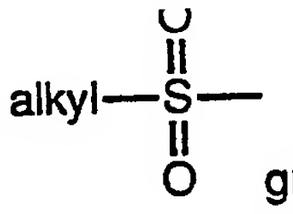
"Aroylamino" is an aroyl-NH- group.

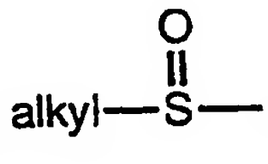
"Halo" means fluoro, chloro, bromo, or iodo.

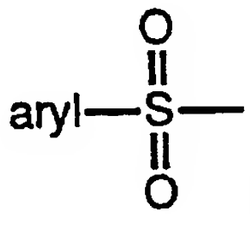
"Hydroxyalkyl" means an HO-alkyl- group. Preferred groups include hydroxymethyl and hydroxyethyl.

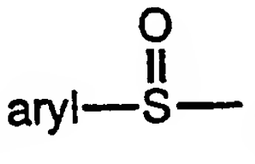
"Aralkylsulfonyl" means an  group.

"Aralkylsulfinyl" means an  group.

"Alkylsulfonyl" means an  group. Preferred groups are those in which the alkyl group is lower alkyl.

"Alkylsulfinyl" means an  group. Preferred groups are those in which the alkyl group is lower alkyl.

"Arylsulfonyl" means an  group.

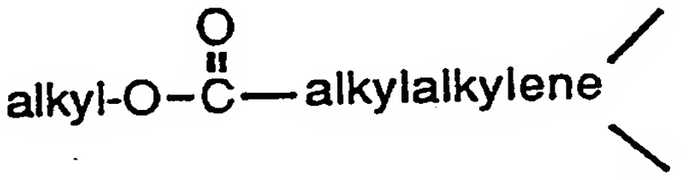
"Arylsulfinyl" means an  group.

"Heterocyclyl" means about a 4- to about a 15- membered monocyclic or multicyclic ring system in which one or more of the atoms in the ring or rings is an element other than carbon, for example nitrogen, oxygen or sulfur. "Substituted heterocyclyl" means a heterocyclyl group substituted by one or more aryl group substituents. Preferred heterocyclyl groups include pyridyl, quinolinyl, and isoquinolinyl.

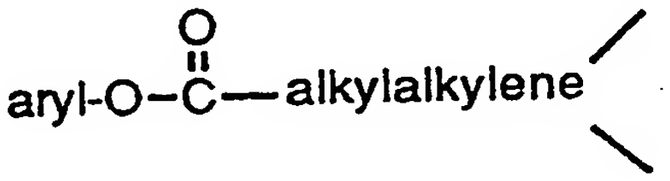
"Nitrogen-containing heterocyclyl" means a heterocyclyl group which contains at least one basic nitrogen atom in the ring or rings, and which is

attached by that basic nitrogen atom. "Substituted nitrogen-containing heterocyclyl" means a nitrogen-containing heterocyclyl group substituted by one or more aryl group substituents.

"Carboxyalkylalkylene" means an group. Preferred groups include carboxymethylmethylene and carboxyethylmethylene.

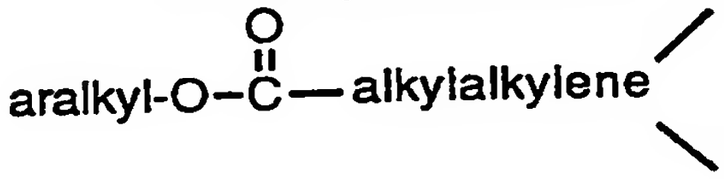


"Alkoxycarbonylalkylalkylene" means an group. Preferred groups include methoxy- and ethoxy- carbonylmethyl- and carbonylethyl- methylene.



"Aryloxycarbonylalkylalkylene" means an group. Preferred groups include phenoxycarbonylmethyl- and phenoxycarbonylethyl- methylene.

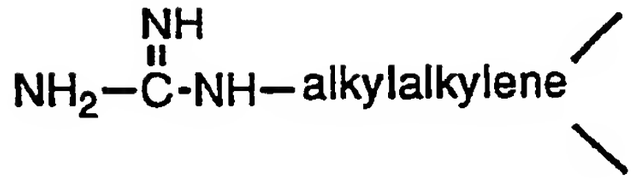
"Aralkoxycarbonylalkylalkylene" means an



group. Preferred groups include benzyloxycarbonylmethyl- and benzyloxycarbonylethyl- methylene.

"Carbamoylakylalkylene" means an group. Preferred groups include carbamoylmethyl- and carbamoylethyl- methylene.

"Alkylthioalkylalkylene" means an group. A preferred group is methylthioethylmethylene.



"Guanidinoalkylalkylene" means an group. Preferred groups include guanidinopropyl- and guanidinobutyl-methylene.

"Aminoalkylalkylene" means an group. Preferred groups include aminopropyl- and aminobutyl- methylene.

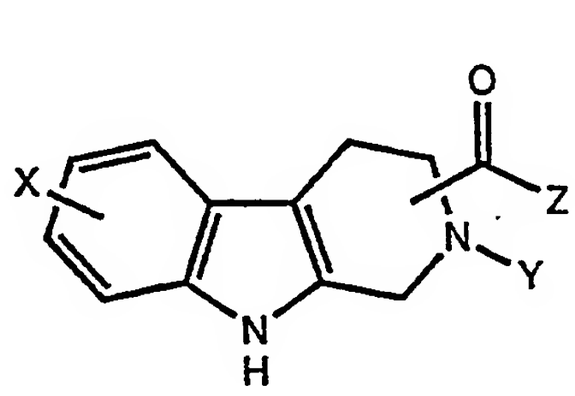
carboxymethyl and carboxyethyl.

"Alkoxycarbonylalkyl" means an alkyl-O-C-alkyl- group. Preferred groups include methoxy- and ethoxy- carbonylmethyl and carbonyl ethyl.

"Aryloxycarbonylalkyl" means an aryl-O-C-alkyl- group. Preferred groups include phenoxycarbonyl- methyl and ethyl.

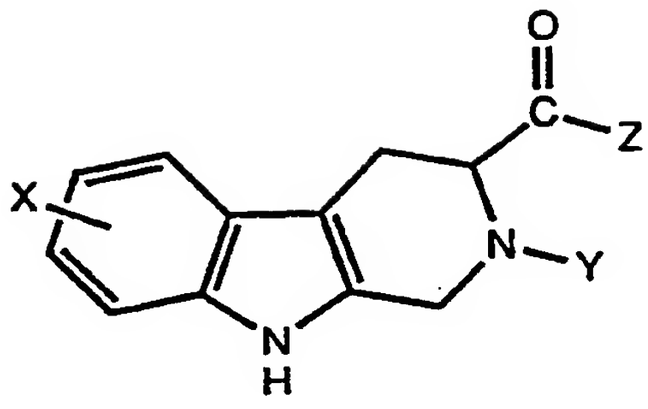
"Aralkoxycarbonylalkyl" means an aralkyl-O-C-alkyl- group. Preferred groups include benzyloxy- methyl and ethyl.

A preferred class of compounds of the present invention is described by Formula II below.



Formula II

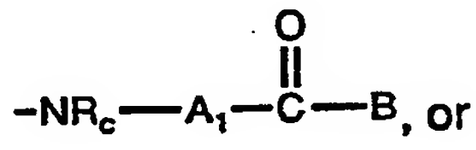
A more preferred class of compounds of the present invention is described by Formula III below.

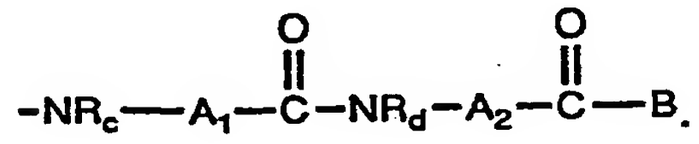


Formula III

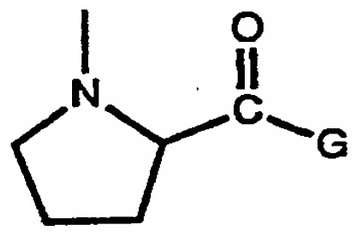
A still more preferred class of compounds of the present invention is described by Formula III wherein Z is

$-NR_aR_b$,

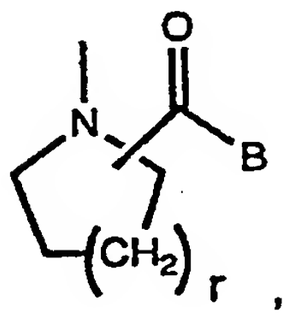


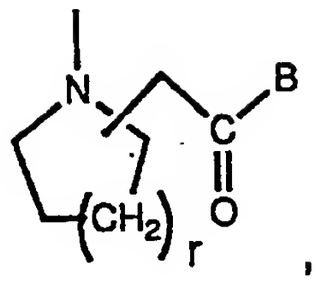


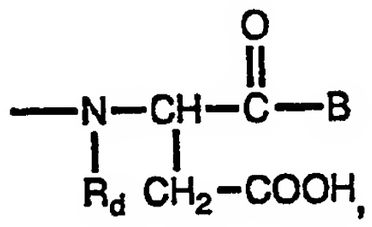
A most preferred class of compounds of the present invention is described by Formula III wherein Z is

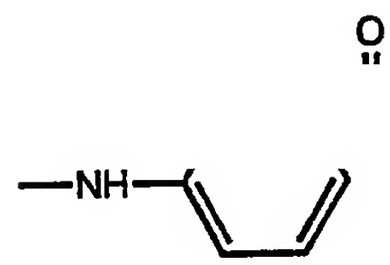


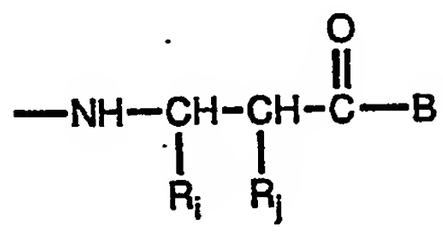
where G is











where

B is hydroxy, alkoxy, aralkoxy, aryloxy or $-NR_fR_g$ where R_f and R_g are independently hydrogen, alkyl, or aralkyl; and

R_i and R_j are independently hydrogen, or alkyl.

Another most preferred class of compounds of the present invention is described by the still more preferred class of compounds wherein Y is substituted or unsubstituted aroyl, alkylcarbamoyl, substituted or unsubstituted arylcarbamoyl, substituted or unsubstituted N-alkyl arylcarbamoyl, alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, or substituted or unsubstituted aralkoxycarbonyl.

A special embodiment of the present invention is described by the still more preferred class of compounds wherein Y is substituted or unsubstituted aroyl, alkylcarbamoyl, substituted or unsubstituted arylcarbamoyl, or substituted or unsubstituted aryloxycarbonyl.

Another special embodiment of the present invention is described by the still more preferred class of compounds wherein Y is substituted or unsubstituted arylcarbamoyl.

The compounds of the present invention contain asymmetric centers. These asymmetric centers may independently be in either the R or S configuration. The present invention comprises the individual stereoisomers and mixtures thereof.

The compounds of the present invention may be useful in the form of the free base or acid or in the form of a pharmaceutically acceptable salt thereof. All forms are within the scope of the invention.

Where the compound of the present invention is substituted with a basic moiety, acid addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the animal organism in pharmaceutical doses of the salts, so that the beneficial gastrin and cholecystokinin antagonist properties inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures.
Pharmaceutically acceptable salts within the scope of the invention are those derived from the following acids: mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesufonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like. The corresponding acid addition salts comprise the following: hydrochloride, sulfate, phosphate, sulfamate, acetate, citrate, lactate, tartarate, malonate, methanesulfonate,

ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate respectively.

The acid addition salts of the compounds of this invention are prepared either by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

moiety, base addition salts may be formed and are simply form for use; and in practice, use of the salt form inherently amounts to use of the free acid form. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the animal organism in pharmaceutical doses of the salts, so that the beneficial gastrin and cholecystokinin antagonistic properties inherent in the free acid are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts within the scope of the invention are those derived from the following bases: sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, tetramethylammonium hydroxide, and the like.

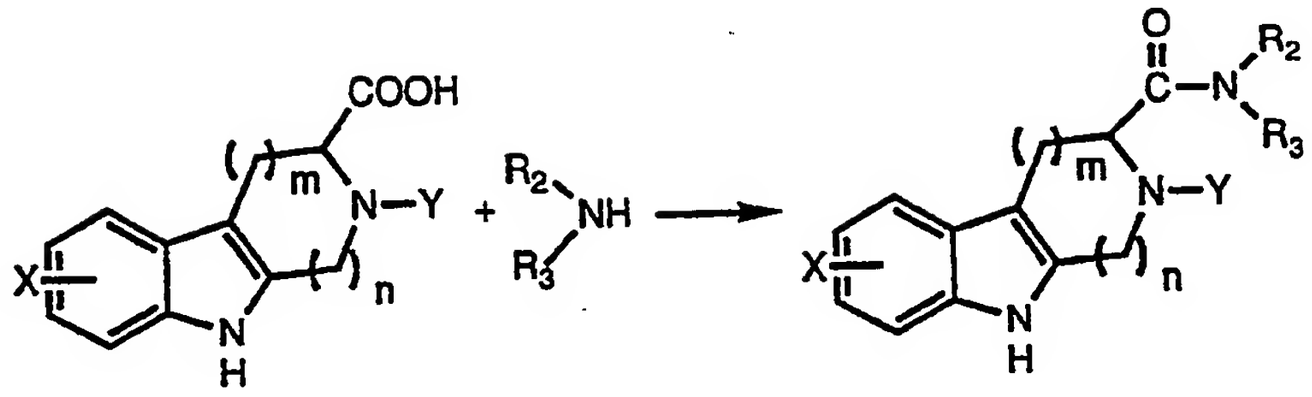
Metal salts of compounds of the present invention may be obtained by contacting a hydroxide, carbonate or similar reactive compound of the chosen metal in an aqueous solvent with the free acid form of the compound. The aqueous solvent employed may be water or it may be a mixture of water with an organic solvent, preferably an alcohol such as methanol or ethanol, a ketone such as acetone, an aliphatic ether such as tetrahydrofuran, or an ester such as ethyl acetate. Such reactions are normally conducted at ambient temperature but they may, if desired, be conducted with heating.

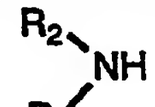
Amine salts of compounds of the present invention may be obtained by contacting an amine in an aqueous solvent with the free acid form of the compound. Suitable aqueous solvents include water and mixtures of water with alcohols such as methanol or ethanol, ethers such as tetrahydrofuran, nitriles such as acetonitrile, or ketones such as acetone. Amino acid salts may be similarly prepared.

Compounds of this invention may be prepared in accordance with the reaction sequences described below, or can be prepared by methods known in the art. The starting materials used in the preparation of compounds of this invention are known or are commercially available, or can be prepared by known methods or by specific reaction schemes described herein.

The compounds of the present may be prepared, generally, by the procedure shown in Scheme I below.

Scheme I



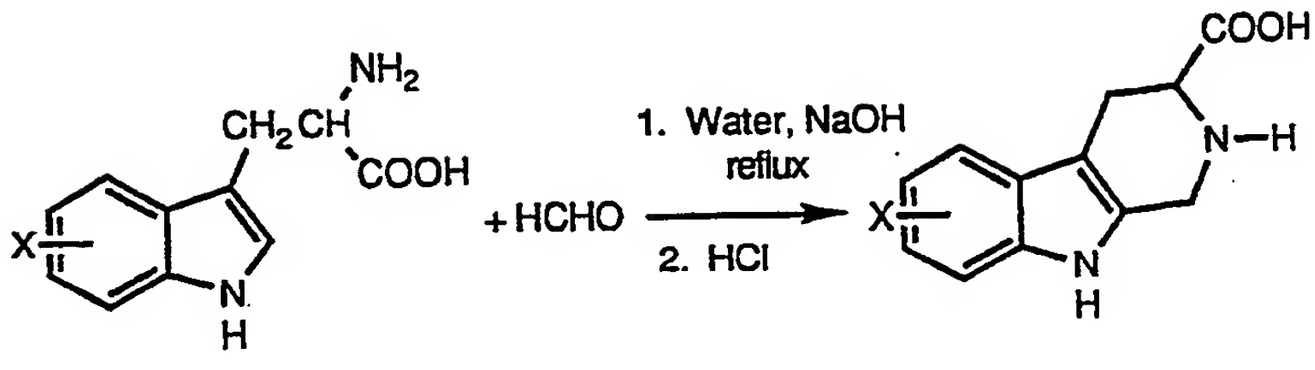
tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid, or analogue or derivative thereof. Y represents either the desired substituent for the final product, or may be an appropriate blocking group to prevent cross reaction during the coupling procedure. Such blocking groups include, but are not limited to, tert-butoxycarbonyl (BOC), carbobenzoxy (CBZ), and benzyl. The blocking group may then be retained or removed to give the final product, or the deprotected indole may be further derivatized to give the final product. The amine derivative,  , is Z'H where Z' is Z as defined above, or a protected derivative thereof or precursor moiety thereto. Since the amine derivative may be an amino acid or peptide, or a derivative of an amino acid or peptide, it may also be protected by appropriate blocking groups to prevent cross reaction during the coupling. These protecting groups may likewise be retained or removed by standard methods subsequent to the coupling reaction to give the final product.

The coupling may be effected by methods generally used in peptide synthesis (see for example, M. Bodanszky and A. Bodanszky, The Practice of Peptide Synthesis, Springer-Verlag, 1984) or other methods of amide bond formation. One such method involves coupling in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), in the presence of 1-hydroxybenzo-triazole (HBT) and triethylamine in an appropriate solvent such as dimethylformamide (DMF), at room temperature. Another method is that of C. Van der Auwera, et al. *Int. J. Peptide Protein Res.*, **29**, 574-588 (1987), whereby the coupling is done in the presence of N,N-bis[2-oxo-3-

oxazolinyl]phosphorodiamidic chloride (BOP-Cl), at reduced temperatures in solvents including DMF and tetrahydrofuran (THF). The coupling may also proceed through in situ formation of a mixed anhydride of the carboxylic acid, such as using isopropyl chloroformate in the presence of N-methyl piperidine, followed by reaction with the amine, (see, N. Leo Benoiton, et al., *Int. J. Peptide Protein Res.* **31**, 577-580 (1988)).

The 1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid is available from the corresponding tryptophan, or derivative of tryptophan, as shown in Scheme II below.

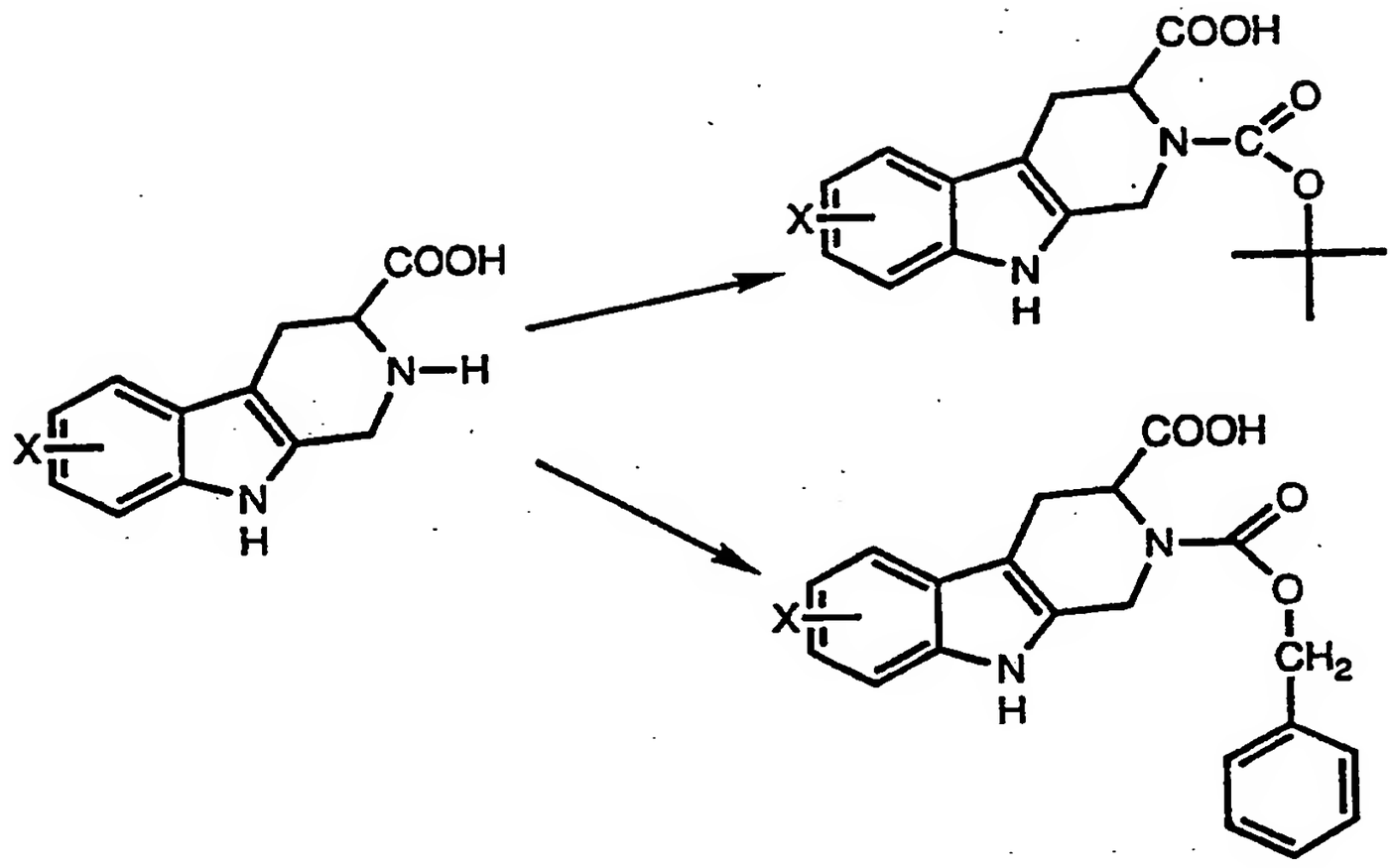
Scheme II



The tryptophan derivative is refluxed with formaldehyde in water in the (see, Lippke, et al., *J.Med. Chem.*, 26, 499-503 (1983)). It should be noted this reaction proceeds with retention of stereochemistry of the tryptophan. Thus, if the starting material is of the D- or L- configuration, the resulting product will be of the (R) or (S) configuration, respectively (see, J. Sandrin, et al., *J. Org. Chem.*, **54**, 5636-5640 (1989)).

The basic amine nitrogen of the ring may then be protected by standard methods, examples of which are shown in Scheme III below.

Scheme III

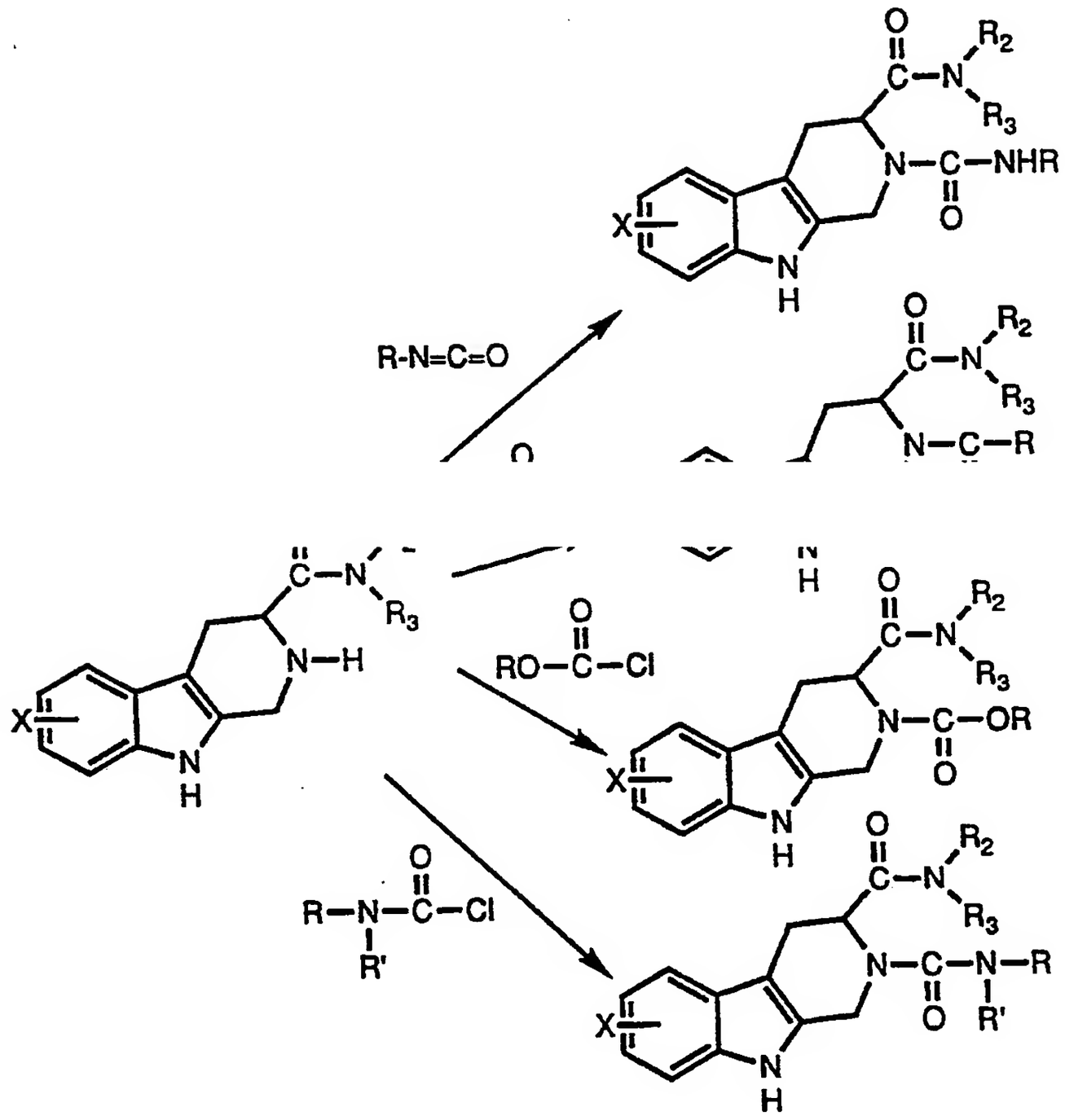


The BOC group may be introduced by treating the carboline with di-t-butyl dicarbonate in the presence of sodium carbonate or potassium carbonate in solution of tetrahydrofuran and water. Likewise the CBZ group may be introduced using benzyl chloroformate in place of di-t-butyl dicarbonate.

The amine derivative to be used in the coupling reaction may be an aliphatic or aromatic amine or an amino acid, peptide, or amino acid or peptide derivative or analogue. The amines, amino acids, peptides or derivatives are available commercially or may be prepared by standard organic chemical or peptide synthetic techniques.

Following the coupling reaction, the blocking group on the ring nitrogen may be removed. In the case of the BOC group, this may be accomplished by treatment with trifluoroacetic acid. The CBZ group may be removed under catalytic hydrogenolysis conditions, such as treatment with hydrogen in ethanol or methanol in the presence of a palladium on carbon catalyst. After deprotection, further derivatization may be accomplished if desired, as shown in Scheme IV below.

Scheme IV



A carbamoyl function may be introduced by treating the deprotected compound with the appropriate alkyl or aryl isocyanate in a solvent such as THF or DMF. An acyl or aroyl function may be introduced by treatment with the appropriate acid halide, in solvents such as THF or methylene chloride, in the presence of a base such as triethylamine. An aryloxycarbonyl function may be introduced by treatment with the appropriate aryl chloroformate derivative in the presence of an organic base such as triethylamine inn an organic solvent such as THF or methylene chloride. A N,N disubstituted carbamoyl group, such as an N-alkyl arylcarbamoyl group may be introduced by treatment with the appropriate carbamoyl chloride in the presence of an organic base such as triethylamine in an organic solvent such as THF or methylene chloride.

If protecting groups are necessary to prevent cross reaction with the side chain at the 3-position, these could be retained or removed by standard procedures to give the final product.

As noted above, compounds of the present invention have asymmetric carbon atoms which may, individually, be in either the R or S configuration. As a result, the compounds may be obtained as individual enantiomers, racemic mixtures, or, when two or more asymmetric carbon atoms are present, as a mixture of diastereomers. The product may be synthesized as a mixture of isomers and then the desired isomer separated by conventional techniques such as chromatography or fractional crystallization in the case where diastereomers are to be separated, or by chiral chromatography or separation of diastereomeric salts or derivatives of the isomers by fractional crystallization or chromatography in the case enantiomers, followed by reisolation of the desired product by conventional techniques. Alternatively, synthesis of the compounds may be carried by known stereospecific processes, or by using the appropriate form of intermediates which would result in obtaining the desired stereoisomer.

The present invention is further explained by the following illustrative examples.

Example 1

N-[(3R)-1,2,3,4-Tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide

Step 1: N-BOC-L-aspartic acid amide ß-benzyl ester

26.2 g N-BOC-L-aspartic acid ß-benzyl ester is dissolved in 500 ml anhydrous tetrahydrofuran and 8.2 g 4-methylmorpholine is added to the solution which is then cooled to -15°C. 8.80 g ethyl chloroformate is added over 5 minutes and the mixture stirred at -15°C for 45 minutes. 5.45 ml of concentrated ammonium hydroxide solution (28-30%) is added and the mixture is stirred at room temperature for 17 hours. The mixture is then evaporated in vacuo and the residue taken up in 2.2 L of ethyl acetate. The ethyl acetate solution is washed with sodium carbonate solution, water, brine,

dried over sodium sulfate, filtered and evaporated in vacuo. The residue is stirred in ether and the resulting solid collected by filtration to give the desired product, m.p. 158-159°C.

Step 2: L-aspartic acid amide ß-benzyl ester trifluoroacetate

220 ml of trifluoroacetic acid is cooled in an ice bath and 22.0 g BOC-L-aspartic acid amide ß-benzyl ester is added over a period of 5 minutes. The solution is stirred at room temperature for 1 hour, evaporated in vacuo and the residue triturated in ether to give the desired product.

10.0 g L-aspartic acid amide ß-benzyl ester trifluoroacetate, 6.88g BOC-L-leucine, 5.98 g 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), and 4.22 g 1-hydroxybenzotriazole (HBT) are dissolved together in 50 ml dimethylformamide followed by the addition of 6.30 g triethylamine. The mixture is stirred at room temperature for 18 hours, then evaporated in vacuo at 40°C/1 mm Hg. The residue is taken up in 500 ml of ethyl acetate and washed with 10% citric acid solution, 10% sodium carbonate solution, water, brine, and dried over sodium sulfate. The solution is filtered, evaporated and the residue triturated in ether to give the desired product as a solid.

Step 4: L-leucyl-L-aspartic acid amide ß-benzyl ester

7.37 g BOC-L-leucyl-L-aspartic acid amide ß-benzyl ester is stirred into 75 ml trifluoracetic acid which had been cooled in an ice bath. The ice bath is removed and the solution stirred at room temperature for 45 minutes. The solution is evaporated in vacuo and the oil residue dissolved in 200 ml of ethyl acetate. The solution is washed with sodium carbonate solution, dried over sodium sulfate, filtered, evaporated, and the residue triturated with ether to give the desired product, m.p. 89-94°C.

Step 5: (3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid

20.0 g D-tryptophan is suspended in 40 ml of water and 7.83 g 50%(w/w) sodium hydroxide solution is added and this mixture is stirred to give

a clear solution. 7.95 g 37% formaldehyde is added and this mixture is stirred for 2 hours at room temperature, then refluxed for 3 hours. The hot solution is poured into 200 ml water and, with vigorous stirring, the pH is adjust to 5 with 6N hydrochloric acid, giving a precipitate. The slurry is stirred for 18 hours, filtered, and the solid dried at 70°C/0.1mm Hg overnight to give 18.5 g of the desired product.

Step 6: (3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid

8.73 g di-t-butyl dicarbonate and 8.65 g (3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid are dissolved together in 150 ml tetrahydrofuran and 5.53 g potassium carbonate is added along with 150 ml of water. The mixture is stirred vigorously overnight. The mixture is evaporated in vacuo to remove most of the THF and the aqueous residue is acidified with 1N hydrochloric acid. This is extracted with ethyl acetate and the organic solution washed with brine, dried over sodium sulfate, filtered, and evaporated. The residue is evaporated from acetonitrile to give the desired product.

Step 7: N-[(3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide-ß-benzyl ester

0.47 g (3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid, 0.50 g L-leucyl-L-aspartic acid amide ß-benzyl ester, 0.211 g HBT, and 0.299 g EDC are dissolved together in 2.5 ml dimethylformamide followed by the addition of 0.158 g triethylamine. The mixture is stirred at room temperature overnight, then evaporated in vacuo. The residue is taken into 50 ml ethyl acetate and the solution washed with 10% citric acid solution, 10% sodium carbonate solution, water, brine, and dried over sodium sulfate. The solution is filtered, evaporated to give the desired product.

Step 8: N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide ß-benzyl ester

0.85 g N-[(3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido-[3,4,-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide-ß-benzyl ester is dissolved in 8.5 ml trifluoroacetic acid and stirred at room temperature for 30 minutes. The

solution is evaporated in vacuo and the residue stirred with 10% sodium carbonate solution/ethyl acetate, giving a solid which is collected, washed and dried giving 0.56 g of the desired product, m.p. 189-191°C.

Step 9: N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide

0.51 g of the product from Example 1, Step 8, is dissolved in 200 ml methanol and 0.10 g 10% palladium on carbon is added. The mixture is stirred under hydrogen at atmospheric pressure for 3 hours. The mixture is filtered, resulting solid collected to give 0.26 g of the desired product, m.p. [illegible]

Example 2

N-[(3S)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide

Step 1: (3S)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid

When L-tryptophan is substituted for D-tryptophan in Example 1, Step 5, the desired product is obtained.

Step 2: N-[(3S)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide

When (3S)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid is substituted for the acid in Example 1, Step 6, and the resulting product treated as in Example 1, Steps 7, 8, and 9, the desired product is obtained, m.p. 202-205°C.

Example 3

N-[(3R)-1,2,3,4-Tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-aspartic acid amide

Step 1: (3R)-2-CBZ-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid

5.00 g (3R)-1,2,3,4-Tetrahydro-9H-pyrido[3,4-b]-indole-3-carboxylic acid is suspended in 50 ml water/50 ml tetrahydrofuran and 5.15 g sodium carbonate is added. The mixture is stirred for 5 minutes and 3.94 g benzyl chloroformate is added and the mixture stirred overnight. The mixture is evaporated in vacuo to remove the THF, the aqueous residue acidified with 1N hydrochloric acid and the resulting solid extracted into ethyl acetate. The organic solution is washed with 1N HCl, water, brine, and dried over sodium sulfate. The solution is filtered, evaporated and the residue crystallized from toluene to give the desired product, m.p. 181-184°C.

Step 2: N-[(3R)-2-CBZ-1,2,3,4-tetrahydro-9H-pyrido-[3,4-b]indole-3-carbonyl]-L-aspartic acid amide ß-benzyl ester

1.00 g (3R)-2-CBZ-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid, 0.96 g L-aspartic acid amide ß-benzyl ester trifluoroacetate, 0.405 g HBT and 0.574 g EDC is dissolved in 4 ml of dimethylformamide, 0.61 g triethylamine is added and the mixture stirred at room temperature overnight. The mixture is worked up as in Example 1, Step 3, and the crude product so obtained is purified by flash chromatography on silica gel in ethyl acetate to give the desired product.

Step 3: N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]-indole-3-carbonyl]-L-aspartic acid amide

1.10 g of the product from Example 3, Step 2, is dissolved in 100 ml methanol and 0.10 g 10% palladium on carbon is added. The mixture is stirred under hydrogen at atmospheric pressure for 5 hours, filtered, evaporated and the residue purified by flash chromatography on silica gel in ethyl acetate/methanol/water, 6:3:1, to give the desired product, m.p. 200-202°C.

Example 4

N-[(3S)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-aspartic acid amide

When (3S)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid is substituted for the acid in Example 3, Step 1, and the resulting product treated as in Example 3, Steps 2, and 3, the desired product is obtained, m.p. 177-181°C.

Example 5

(3R)-3-(2,2-Diphenyl)ethylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

1.00 g (3R)-2-CBZ-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid, 0.536 g 2,2-diphenyl-ethylamine, 0.574 g EDC and 0.404 g HBT are dissolved together in 4 ml of dimethylformamide, 0.303 g of triethylamine added, and the mixture stirred at room temperature for 18 hours. The mixture is evaporated and the residue taken up in ethyl acetate and this washed with 10% citric acid solution, 10% sodium carbonate, water, brine, and dried over sodium sulfate. The solution is filtered and evaporated to give the desired product.

Step 2: (3R)-3-(2,2-diphenyl)ethylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

1.40 g of the product from Example 5, Step 1, is dissolved in 40 ml of absolute ethanol, 0.14 g 10% palladium on carbon added, and the mixture stirred under hydrogen at atmospheric pressure for 3 hours. The mixture is filtered, evaporated and the residue stirred with boiling ethyl acetate, cooled and filtered to give the desired product, m.p. 208-209°C.

Example 6

(3R)-3-Diphenylmethylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

Step 1: (3R)-2-BOC-3-diphenylmethylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

1.58 g (3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid, 0.915 g aminodiphenyl-methane, 1.01 g EDC, and 0.709 g HBT are dissolved together in 6 ml DMF and 0.53 g triethylamine is added. The mixture is stirred at room temperature overnight and worked as in Example 5, Step 1 to give 2.20 g of the desired product.

Step 2: (3R)-3-diphenylmethylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

2.10 g of the product from Example 6, Step 1, is dissolved in 21 mol of trifluoroacetic acid and the solution stirred at room temperature for 1 hour. The solution is evaporated and the residue dissolved in ethyl acetate. This solution is washed with sodium carbonate solution, water, brine and dryed over sodium sulfate. The solution is filtered, evaporated and the residue crystallized from ethanol to give the desired product, m.p. 191-196°C.

Example 7

N-[(3R)-2-benzoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]-indole-3-carbonyl]-L-aspartic acid amide ß-benzyl ester

Step 1: N-[(3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-aspartic acid amide ß-benzyl ester

1.00 g (3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid, 1.06 g L-aspartic acid ß-benzyl ester trifluoroacetate, 0.636 g EDC, and 0.449 g HBT are combined in 5 ml of DMF, along with 0.68 g triethylamine and treated as in Example 3, Step 2, to give the desired product.

Step 2: N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-aspartic acid amide ß-benzyl ester

1.04 g of the product from Example 7, Step 1, is dissolved in 10 ml trifluoroacetic acid and stirred at room temperature for 15 minutes. The solution is evaporated and the residue stirred with 25 ml 10% sodium

carbonate solution. The resulting solid is collected, washed with water, and dried to give the desired product.

Step 3: N-[(3R)-2-benzoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-aspartic acid amide ß-benzyl ester

0.50 g of the product from Example 7, Step 2, and 0.33 g triethylamine are dissolved together in 20 ml tetrahydrofuran, and 0.18 g benzoyl chloride is added. The mixture is stirred at room temperature for 20 minutes. The mixture is evaporated and the residue taken up in 50 ml ethyl acetate and this solution is washed with 1N HCl, water, brine, and dried over sodium sulfate. This desired product, which contained 1.2% (w/w) water, m.p. 110-120°C. Elemental analysis: Calc'd: C, 67.84; H, 5.51; N, 10.55; Found: C, 67.86; H, 5.53; N, 10.29.

Example 8

N-[(3R)-2-benzoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]-indole-3-carbonyl]-L-aspartic acid amide

0.45 g of N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-aspartic acid amide and 0.41 g triethylamine are dissolved together in 4 ml of water/ tetrahydrofuran (1:1). 0.21g benzoyl chloride is added and the solution stirred for 30 minutes. The solution is evaporated and the residue stirred with 1N HCl to give a solid. The solid is dissolved in 0.5 N NaOH and the solution is washed with ethyl acetate. The solution is then acidified, extracted with ethyl acetate and the organic solution is washed with water, brine, dried and evaporated. The residue is triturated in ether to give the desired product as a white solid, m.p. 160°C (dec.).

Example 9

N-[(3R)-2-benzoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide

When N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]-indole-3-carbonyl]-L-leucyl-L-aspartic acid amide is substituted for the amide in Example 8, the desired product is obtained, m.p. 155-160°C.

Example 10

N-[(3R)-2-(2-naphthoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide

When 2-naphthoyl chloride is substituted for benzoyl chloride in Example 9, the desired product is obtained, m.p. 162-166°C.

Example 11

N-[(3R)-2-(3-Methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide

Step 1: N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido-[3,4-b]indole-3-carbonyl]-L-leucyl-aspartic acid amide ß-benzyl ester

0.30 g N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]-indole-3-carbonyl]-L-leucyl-L-aspartic acid amide-ß-benzyl ester is dissolved in 4 ml of dimethylformamide, 0.075 g m-tolylisocyanate is added and the solution stirred at room temperature for 1 hour. The solution is evaporated at 40°C/2 mmHg, the residue dissolved in ethyl acetate and this solution washed with water, brine, and dried over sodium sulfate. The solution is filtered, evaporated to the desired product, which is used, without further treatment, for the next step.

Step 2: N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide

0.31 g of the product from Example 11, Step 1, is dissolved in 9 ml absolute ethanol. 0.03 g of 10% palladium on carbon is added and the mixture stirred under hydrogen at room temperature for 3 hours. The mixture is filtered, evaporated, and the residue stirred with 20 ml ether for 3 hours and the resulting solid collected by filtration to give 0.20 g of the desired product, m.p. 154-157°C.

Example 12

N-[(3S)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide

When N-[(3S)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]-indole-3-carbonyl]-L-leucyl-L-aspartic acid amide ß-benzyl ester is substituted for the ester in Example 11, Step 1, and the resulting product treated as in Example 11, Step 2, the desired product is obtained, m.p. 191-193°C.

Example 13

(3R)-3-(N,N-Dipentylcarbamoyl)-2-(3-methylphenyl-carbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

Step 1: (3R)-2-BOC-3-(N,N-dipentylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

0.40 g (3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid is dissolved in 10 ml tetrahydrofuran. The solution is cooled to -15°C and 0.127 g triethylamine and 0.386 g N,N-bis[2-oxo-3-oxazolinyl]phosphorodiamidic chloride (BOP-Cl) is added. The mixture is stirred at -15°C for 20 minutes, then evaporated in vacuo to one-half of the original volume. The mixture is cooled in an ice bath and 0.239 g dipentylamine is added. The mixture is stirred in ice bath temperature overnight. The mixture is evaporated and the residue taken into 50 ml of ethyl acetate and this solution is washed with 1N HCl, 10% sodium bicarbonate solution, water, brine and dried over sodium sulfate. The solution is filtered and evaporated to give the desired product.

Step 2: (3R)-3-(N,N-dipentylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

0.33 g of the product from Example 13, Step 1, is dissolved in 4 ml trifluoroacetic acid and stirred at room temperature for 30 minutes. The solution is evaporated and the residue dissolved in ethyl acetate and the

organic solution washed with sodium carbonate solution, water, brine and dried over sodium sulfate. The solution is filtered, evaporated, and the residue stirred with ether to give the desired product as a solid, , m.p. 157-158°C.

Step 3: (3R)-3-(N,N-dipentylcarbamoyl)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

0.114 g (3R)-3-(N,N-dipentylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole is dissolved in 2 ml tetrahydrofuran and 42.7 mg of m-tolylisocyanate is added. The solution is stirred at room temperature for 1 hour, evaporated, and the residue triturated with hexane to give 0.119 g of the desired product, m.p. 154-155°C.

Example 14

N-[(3R)-2-Phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide

When phenylisocyanate is substituted for m-tolylisocyanate in Example 11, Step 1, and the resulting product treated as in Example 11, Step 2, the desired product is obtained, m.p. 170°C (dec.).

Example 15

Ethyl 4-N-[(3R)-2-carbobenzoxy-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]aminobenzoate

0.50 g (3R)-2-CBZ-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid is dissolved in 14 ml of tetrahydrofuran/2 ml dimethylformamide, and the mixture cooled to 0°C. 0.14 g N-methyl piperidine, then 0.17 g isopropyl chloroformate are added and the mixture stirred in ice for 5 minutes. 0.22 g ethyl-p-amino benzoate is added and the mixture stirred at room temperature overnight. The mixture is poured into 1N HCl, extracted with ethyl acetate and the organic solution washed with sodium bicarbonate solution, water and brine and dried over magnesium sulfate. The solution is filtered and evaporated and the residue purified by flash chromatography on

silica gel in acetone/methylene chloride (1:9) to give the desired product, m.p. 76-79°C.

Example 16

Ethyl 3-N-[(3R)-2-carbobenzoxy-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]aminobenzoate

When ethyl-3-aminobenzoate is substituted for ethyl-4-aminobenzoate in Example 15, the desired product is obtained, m.p. 78-81°C.

Example 17

Ethyl 2-N-[(3R)-2-carbobenzoxy-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]aminobenzoate

When ethyl-2-aminobenzoate is substituted for ethyl-4-aminobenzoate in Example 15, the desired product is obtained as the hemihydrate, m.p. 79-82°C.

Example 18

(3R)-2-carbobenzoxy-3-(2-pyrrolidin-1-ylcarbonyl)phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

Step 1: N-(2-aminobenzoyl)pyrrolidine

17.5 g isatoic anhydride and 2.66 g 4-dimethylaminopyridine are combined in 500 ml tetrahydrofuran. 9.32 g of pyrrolidine is added and the mixture is heated at reflux overnight. The mixture is concentrated in vacuo, the residue taken into ethyl acetate and the organic solution washed with citric acid solution, water and brine and dried over magnesium sulfate. The solution is filtered, evaporated and the residue triturated in ether/hexane (1:5) to give the desired product, m.p. 79-81°C.

Step 2: (3R)-2-CBZ-3-(2-pyrrolidin-1-ylcarbonyl)phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

When N-(2-aminobenzoyl)pyrrolidine is substituted for ethyl-4-aminobenzoate in Example 15, the desired product.is obtained, m.p. 95-98°C.

Example 19

(3S)-2-carbobenzoxy-3-(2-pyrrolidin-1-ylcarbonyl)phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

When (3S)-2-CBZ-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]-indole-3-carboxylic acid is substituted for the acid in Example 18, Step 2, the desired product is obtained, m.p. 77-80°C.

Example 20

(3R)-2-(2-naphthoyl)-3-(2-pyrrolidin-1-ylcarbonyl)phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

Step 1: (3R)-3-(2-pyrrolidin-1-ylcarbonyl)phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

0.80 g of (3R)-2-CBZ-3-(2-pyrrolidin-1-ylcarbonyl)phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole is dissolved in 10 ml of methanol and 9.20 g 10% palladium on carbon is added. The solution is stirred under hydrogen at atmospheric pressure at room temperature overnight. The mixture is filtered and evaporated to give the desired product.

Step 2: (3R)-2-(2-naphthoyl)-3-(2-pyrrolidin-1-ylcarbonyl)phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

0.150 g of the product from Example 20, Step 1, is dissolved in 5 ml methylene chloride and the solution cooled to 0°C. 0.012 g triethylamine is added, followed by the addition of 0.08 g 2-naphthoyl chloride. The mixture is stirred at 0°C for 1 hour, then at room temperature overnight. The mixture is concentrated in vacuo. The residue is taken up in ethyl acetate and the organic solution is washed with citric acid solution, saturated sodium

bicarbonate solution and brine and dried over magnesium sulfate. This is filtered and evaporated to a solid, to give the desired product, m.p. 113-115°C.

Example 21

(3R)-2-(4-methoxy)phenylcarbamoyl-3-(2-pyrrolidin-1-ylcarbonyl)phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole

0.150 g of (3R)-3-(2-pyrrolidin-1-ylcarbonyl)phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole is dissolved in 5 ml anhydrous methylene [illegible] is added. The residue dissolved in ethyl acetate. The organic solution is washed with 1N HCl, water and brine and dried over magnesium sulfate, filtered and evaporated to obtain a residue. The residue is triturated in ether to give the desired product, m.p. 159-162°C.

Example 22

2-[N-[(3R)-2-carbobenzoxy-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]]amino-N,N-dibutylbenzamide

Step 1: 2-amino-N,N-dibutylbenzamide

2.0 g isatoic anhydride is dissolved in 50 ml methylene chloride/5 ml dimethylformamide and 1.87 g 4-dimethylaminopyridine and 1.98 g dibutylamine are added. The mixture is stirred at room temperature for 5 hours, then diluted with 250 ml of ethyl acetate. The organic solution is washed with 10% HCl and brine and dried over sodium sulfate followed by filtration and evaporation to obtain a residue. The residue is dissolved in 25 ml ethyl acetate, the solution filtered, concentrated and this residue purified by flash chromatography on silica gel in ethyl acetate/hexane, 2:3, to give the desired product.

Step 2: 2-[N-[(3R)-2-CBZ-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]]amino-N,N-dibutylbenzamide

When 2-amino-N,N-dibutyl benzamide is substituted for ethyl-p-aminobenzoate in Example 15, the desired product is obtained, m.p. 80-81°C.

Example 23

Ethyl 2-N-[(3S)-2-carbobenzoxy-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]aminobenzoate

When (3S)-2-CBZ-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid is substituted for the (3R)-carboxylic acid in Example 17, the desired product is obtained, m.p. 93-94°C.

Example 24

N-(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-isoleucyl-L-aspartic acid amide

Step 1: N-BOC-L-isoleucyl-L-aspartic acid amide β-benzyl ester

When Boc-L-isoleucine is substituted for Boc-L-leucine in Example 1, Step 3, , the desired product is obtained.

Step 2: L-isoleucyl-L-aspartic acid amide β-benzyl ester

Using essentially the procedure of Example 1, Step 4, the desired product is prepared from N-BOC-L-isoleucyl-L-aspartic acid amide β-benzyl ester.

Step 3: N-[(3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-isoleucyl-L-aspartic acid amide-ß-benzyl ester

Using essentially the procedure of Example 1, Step 7, the desired product is prepared from L-isoleucyl-L-aspartic acid amide β-benzyl ester.

Step 4: N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-isoleucyl-L-aspartic acid amide-ß-benzyl ester

Using essentially the procedure of Example 1, Step 8, the desired product is prepared from N-[(3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-isoleucyl-L-aspartic acid amide-ß-benzyl ester .

Step 5: N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-isoleucyl-L-aspartic acid amide

When 3,4-dichlorophenyl isocyanate is substituted for m-tolyl isocyanate and N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-isoleucyl-Step 1, and the resulting product is treated as in Example 1, Step 2, the desired product is obtained, m.p. 155-158°C.

Example 25

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-prolyl-L-aspartic acid amide

When BOC-L-proline is substituted for BOC-L-isoleucine in Example 24, Step 1, and the resulting product treated as in Example 24, Steps 2, 3, 4, and 5, the desired product is obtained, m.p. 141°C.

Example 26

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-1'amino-1'cyclopentyl-carbonyl-L-aspartic acid amide

When BOC-1-amino-1-cyclopentane carboxylic acid is substituted for BOC-L-proline in Example 25, the desired product is obtained, m.p. 168°C.

Example 27

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-ß-alanine

Step 1: BOC-L-leucyl-ß-alanine benzyl ester

When ß-alanine benzyl ester trifluoroacetate is substituted for L-aspartic acid amide β-benzyl ester trifluoroacetate in Example 1, Step 3, the desired product is obtained.

Step 2: L-leucyl-ß-alanine benzyl ester

Using essentially the procedure of Example 1, Step 4, the desired product is obtained from BOC-L-leucyl-ß-alanine benzyl ester.

Step 3: N-[(3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-β-alanine benzyl ester

Using essentially the procedure of Example 1, Step 7, the desired product is prepared from L-leucyl-ß-alanine benzyl ester.

Step 4: N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-β-alanine benzyl ester

Using essentially the procedure of Example 1, Step 8, the desired product is prepared from N-[(3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-β-alanine benzyl ester is prepared.

Step 5: N-(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-ß-alanine

When 3,4-dichlorophenyl isocyanate is substituted for m-tolyl isocyanate and N-[(3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-β-alanine benzyl ester is substituted for the ester in Example 11, Step 1, and the resulting product is treated as in Example 11, Step 2, the desired product is obtained, m.p. 115-117°C.

Example 28

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-glycinamide

Step 1: BOC-L-leucyl-glycinamide

When glycinamide hydrochloride is substituted for L-aspartic acid amide β-benzyl ester trifluoroacetate in Example 1, Step 3, the desired product is obtained.

Step 2: L-leucyl-glycinamide

Using essentially the procedure of Example 1, Step 4, the desired product is prepared from BOC-L-leucyl-glycinamide.

Step 3: N-[(3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-glycinamide

Using essentially the procedure of Example 1, Step 7, the desired product is prepared from L-leucyl-glycinamide.

Step 4: N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-glycinamide

Using essentially the procedure of Example 1, Step 8, the desired product is prepared from N-[(3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-glycinamide.

Step 5: N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-glycinamide

When 3,4-dichlorophenyl isocyanate is substituted for m-tolyl isocyanate and N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-glycinamide is substituted for the ester in Example 11, Step 1, the desired product is obtained, m.p. 142-145°C.

Using appropriate starting materials and procedures analogous to those used in the previous examples, the following compounds are prepared:

Example 29

N-[(3R)-2-(3-methylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-L-O-benzyl-serine, m.p. 176-179°C

Example 30

N-[(3R)-2-(2,3-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-glycinamide, m.p. 136-138°C

Example 31

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucinecyclohexylamide, m.p. 151°C (dec.)

Example 32

N-[(3R)-2-(2,3-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-β-alanine, 97-99°C (dec.)

Example 33

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-glycinamide, m.p. 136-138°C (dec.)

Example 34

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-β-alanine, m.p. 123-125°C (dec.)

Example 35

N-[(3R)-2-(2,3-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-L-aspartic acid amide, m.p. 106-108 °C

Example 36

N-[(3R)-2-(4-methoxyphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-L-aspartic acid amide, m.p. 163°C (dec.)

Example 37

N-[(3R)-2-(3-methylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-isoleucyl-L-aspartic acid amide, m.p. 151-154°C (dec.)

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-D-aspartic acid amide, m.p. 115-118°C (dec.)

Example 39

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucinamide, m.p. 120-122°C

Example 40

N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide-ß-benzyl ester, m.p. 189-191°C

Example 41

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-phenylalanine amide, 141-144°C (dec.)

Example 42

Ethyl 4-N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]aminobenzoate, m.p. 122-124 °C (dec.)

Example 43

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-L-aspartic acid amide, m.p. 166°C (dec.)

Example 44

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-leucyl-D-aspartic acid amide, m.p. 184-185°C

Example 45

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-aspartic acid dipentyl amide, m.p. 104-107°C (dec.)

Example 46

N-[(3R)-2-(naphth-1-ylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide-ß-benzyl ester, m.p. 205°C (dec.)

Example 47

N-[(3R)-2-(naphth-2-ylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide-ß-benzyl ester, m.p. 205°C (dec.)

Example 48

N-[(3S)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-leucyl-D-aspartic acid amide, m.p. 169-170°C

Example 49

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-asparagine, m.p. 156°C (dec.)

Example 50

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-D-aspartic acid amide, m.p. 152°C (dec.)

Example 51

N-[(3S)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-leucyl-L-aspartic acid amide, m.p. 152°C

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]N-methyl-L-leucyl-L-aspartic acid amide, m.p. 159°C

Example 53

N-[(3R)-2-(3-methylbenzoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide, m.p. 147-151°C

Example 54

N-[(3R)-2-(4-chlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-asartic acid amide, m.p. 161-164°C

Example 55

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyido[3,4-b]indole-3-carbonyl]glycyl-L-aspartic acid amide, 127-130°C (dec.)

Example 56

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-leucyl-L-aspartic acid amide, 144-147°C (dec.)

Example 57

N-[(3R)-2-(3-methylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-alanyl-L-aspartic acid amide, m.p. 157-160°C (dec.)

Example 58

N-[(3R)-2-(3,5-dichlorophenylcarbamoyl)-1,2,3,4-tetra-hydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide, m.p. 167°C (dec.)

Example 59

N-[(3R)-2-(3,5-dimethylphenylcarbamoyl)-1,2,3,4-tetra-hydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide, m.p. 159°C (dec.)

Example 60

N-[(3R)-2-(3-methoxyphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide, m.p. 153-156°C (dec.)

Example 61

N-[(3R)-2-(2-naphthylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide, m.p. 146°C (dec.)

Example 62

N-[(3R)-2-(3-trifluoromethylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide, m.p. 165°C (dec.)

Example 63

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-O-benzyl-L-seryl-L-aspartic acid amide, m.p. 138-141°C

Example 64

N-[(3R)-2-(3-fluorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide, m.p. 146-149°C

Example 65

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetra-hydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide, m.p. 162°C

N-[(3R)-2-(1-naphthylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide, m.p. 156-158°C (dec.)

Example 67

N-[(3S)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-prolyl-D-aspartic acid amide, m.p. 174°C (dec.)

Example 68

N-[(3R)-2-(3,4-dichlorobenzoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide

Example 69

N-[(3S)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetra-hydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-prolyl-D-aspartic acid amide, m.p. 174°C

Example 70

N-[(3S)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetra-hydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-leucyl-D-aspartic acid amide, m.p. 164°C

Example 71

N-[(3S)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-leucyl-D-glutamic acid amide

Example 72

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-glutamic acid amide, m.p. 112°C

Example 73

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetra-hydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-glutamic acid amide, m.p. 120°C (dec.)

Example 74

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-β-alanine, m.p. 162°C (dec.)

Example 75

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotic acid

Step 1: benzyl N-BOC-nipecotate

To a solution of N-BOC-nipecotic acid (3.3g) in methylene chloride (70 ml) is added triethylamine (2.0 ml), benzyl alcohol (1.4 ml) and DMAP (1.76g). The solution is cooled to 0°C and isopropenylchloroformate (2.0 ml) is added dropwise and the resulting solution stirred for about 18 hours. The solution is diluted with ethylacetate (200 ml) and the organic layer washed with water, 1N hydrochloric acid, 10% sodium carbonate solution, brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash chromatography, eluting with a gradient of 7% to 15% ethyl acetate in hexane, to give the desired product.

Step 2: benzyl nipecotate

Benzyl N-BOC-nipecotate (4.0g) is dissolved in methylene chloride (60 ml) and trifluoroacetate acid (28.6g) is added. The solution is stirred for 4 hours at room temperature, concentrated in vacuo, and toluene azeotroped twice from the residue to give the desired product as the trifluoroacetate salt.

Step 3: benzyl N-(N-BOC-L-prolyl)nipecotate

Using essentially the procedure of Example 13, Step 1, and purifying the nipecotate and N-BOC-L-proline.

Step 4: benzyl N-(L-prolyl)nipecotate

Using essentially the procedure of Example 75, Step 2, the desired product is prepared from benzyl N-(N-BOC-L-prolyl)nipecotate and isolated as the trifluoroacetate salt.

Step 5: benzyl N-[N-[(3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotate

Using essentially the procedure of Example 13, Step 1, and purifying the crude product by flash chromatography, eluting with 25% ethyl acetate in methylene chloride, the desired is prepared from (3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid and benzyl N-(L-prolyl)nipecotate.

Step 6: benzyl N-[N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotate

Benzyl N-[N-[(3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotate (4.6g) and ethanedithiol (3.52g) are dissolved in methylene chloride (40 ml) and trifluoroacetic acid (17.1g) is added. The solution is stirred at 0°C for about 4 hours and concentrated in vacuo. The residue is dissolved in methylene chloride (200 ml) and the solution stirred with

1N sodium hydroxide solution (30 ml). The organic layer is washed with 3 portions of 1N NaOH, brine, dried over magnesium sulfate, filtered and concentrated in vacuo to give the desired product.

Step 7: benzyl N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotate

Benzyl N-[N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotate (2.0g) is dissolved in methylene chloride (40 ml) and 3,4-dichlorophenylisocyanate (0.73g) is added. The reaction mixture is stirred at room temperature for about 2 hours, concentrated in vacuo, and the residue purified by flash chromatography, eluting with a gradient of 20% to 30% ethyl acetate in methylene chloride, to give the desired product.

Step 8: N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotic acid

Benzyl N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotate (2.3g) is dissolved in tetrahydrofuran (30 ml) and 10% palladium on carbon (0.58g) is added. The mixture is stirred under a hydrogen atmosphere for about 18 hours. The mixture is filtered, and concentrated in vacuo to give the desired product, m.p. 152°C (dec.).

Example 76

N-[N-[(3R)-2-(3,4-dichlorophenoxycarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotic acid

Step 1: 3,4-dichlorophenyl chloroformate

A solution of 3,4-dichlorophenol (1.0g) in toluene (6 ml) is cooled to -15°C and potassium carbonate (0.86g) is added, followed by triphosgene (0.91g) and DMAP (.75g), and the mixture is stirred for about 18 hours. The mixture is filtered and the filtrate concentrated in vacuo. The residue is purified

by flash chromatography, eluting with methylene chloride, to give the desired product.

Step 2: benzyl N-[N-[(3R)-2-(3,4-dichlorophenoxycarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotate

Benzyl N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotate (1.4g) and triethylamine (0.35 ml) are dissolved in methylene chloride (10 ml) and 3,4-dichlorophenyl chloroformate (0.57g) is added. The mixture is stirred at room temperature for is washed with 1N HCl, 10% sodium carbonate solution, magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash chromatography, eluting with a gradient of 50% to 60% ethyl acetate in hexane, to give the desired product.

Step 3: N-[N-[(3R)-2-(3,4-dichlorophenoxycarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotic acid

Using essentially the procedure of Example 75, Step 8, the desired product product, m.p. 146°C (dec.), is prepared from benzyl N-[N-[(3R)-2-(3,4-dichlorophenoxycarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotate.

Example 77

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-(3S)-pyrrolidine-3-carboxylic acid

Step 1: (3R)-3-hydroxypyrrolidine

To a suspension of trans-4-hydroxyproline (10.0g) in cyclohexanol (50 ml) is added 2-cyclohexen-1-one (0.50 ml) and the mixture heated at 200°C for about 18 hours. The mixture is cooled, then diluted with ethyl acetate (500 ml). The solution is extracted with water (3x150 ml) and the aqueous solution concentrated in vacuo to give the crude product which is used, without further treatment, for the next step.

Step 2: N-BOC-(3R)-3-hydroxypyrrolidine

(3R)-3-hydroxypyrrolidine (7.1g) is dissolved in THF (300 ml) and triethylamine (8.25g) is added, followed by di-t-butyl dicarbonate (17.8g) and DMAP (1.0g). The mixture is stirred at room temperature for about 18 hours, and concentrated in vacuo. The residue is dissolved in ethyl acetate (400 ml) and the solution washed with 1N HCl, 10% sodium carbonate solution, brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified by flash chromatography, eluting with a gradient of 35% to 40 % ethyl acetate in hexane, to give the desired product.

Step 3: N-BOC-(3R)-3-hydroxypyrrolidine tosylate

To a solution of N-BOC-(3R)-3-hydroxypyrrolidine (1.7g) in methylene chloride (45 ml) is added triethylamine (0.96g) and DMAP (0.11g), followed by p-toluenesulfonyl chloride (1.73g). The solution is stirred at room temperature for about 18 hours, then diluted with ethyl acetate (400 ml). The organic solution is washed with water, 1N HCl, 10% sodium carbonate solution, brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give the desired product.

Step 4: N-BOC-(3S)-3-cyanopyrrolidine

To a solution of N-BOC-(3R)-3-hydroxypyrrolidine tosylate (2.21g) in dimethylsulfoxide (7 ml) is added sodium cyanide (0.49g) and the mixture heated at 80°C for about 4 hours. 8 ml of 50% saturated aqueous sodium chloride solution is added and the solution extracted with ether. The organic layer is washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash chromatography, eluting with 20% ethyl acetate in hexane, to give the desired product.

Step 5: N-BOC-(3S)-pyrrolidine-3-carboxylic acid

To a solution of N-BOC-(3S)-3-cyanopyrrolidine (0.63g) in ethanol (40 ml) is added 25% aqueous sodium hydroxide (14 ml) and the solution heated at reflux for about 18 hours. The solution is concentrated in vacuo to

about one-third of its total volume and the pH of the remaining solution adjusted to 2 with 6N HCl. The aqueous is extracted with ethyl acetate and the organic layer washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to give the desired product.

Step 6: benzyl N-BOC-(3S)-pyrrolidine-3-carboxylate

Using essentially the procedure of Example 75, Step 1, and purifying the crude product by flash chromatography, eluting with a gradient of 10% to 15% ethyl acetate in hexane, the desired product is prepared from N-BOC-(3S)-

Step 7: benzyl-(3S)-pyrrolidine-3-carboxylate

Using essentially the procedure of Example 75, Step 2, the desired product is prepared, as the trifluoroacetate salt, from benzyl N-BOC-(3S)-pyrrolidine-3-carboxylate.

Step 8: benzyl N-(N-BOC-L-prolyl)-(3S)-pyrrolidine-3-carboxylate

N-BOC-L-proline (0.67g) is dissolved in methylene chloride (25 ml) and N-methylpiperidine (0.33 ml) is added. The solution is cooled to 0°C and isopropenylchloroformate (0.30 ml) is added. After stirring for 2 minutes, a solution of benzyl-(3S)-pyrrolidine-3-carboxylate trifluoroacetate (2.74 mmol) and N-methylpiperidine (0.33 ml) in methylene chloride (5 ml) is added and the solution stirred at room temperature for about 18 hours. The solution is diluted with ethyl acetate and washed with 1N HCl, 10% sodium carbonate solution, and brine. The organic layer is dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue is purified by flash chromatography, eluting with a gradient of 50% to 75% ethyl acetate in hexane to give the desired product.

Step 9: benzyl N-(L-prolyl)-(3S)-pyrrolidine-3-carboxylate

Using essentially the procedure of Example 75, Step 2, the desired was prepared, as the trifluoroacetate salt, from benzyl N-(N-BOC-L-prolyl)-(3S)-pyrrolidine-3-carboxylate.

Step 10: benzyl N-[N-[(3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-(3S)-pyrrolidine-3-carboxylate

Using essentially the procedure of Example 13, Step 1, and purifying the crude product by flash chromatography, eluting with a gradient of 30% to 40% ethyl acetate in methylene chloride, the desired product is prepared from (3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carboxylic acid and benzyl N-(L-prolyl)-(3S)-pyrrolidine-3-carboxylate.

Step 11: benzyl N-[N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-(3S)-pyrrolidine-3-carboxylate

Using essentially the procedure of Example 75, Step 6, the desired product is prepared, as the trifluoroacetate salt, from benzyl N-[N-[(3R)-2-BOC-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-(3S)-pyrrolidine-3-carboxylate.

Step 12: benzyl N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-(3S)-pyrrolidine-3-carboxylate

Using essentially the procedure of Example 75, Step 7, and purifying the crude product by flash chromatography, eluting with a gradient of 20% to 30% ethyl acetate in methylene chloride, the desired product is prepared from benzyl N-[N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-(3S)-pyrrolidine-3-carboxylate.

Step 13: N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-(3S)-pyrrolidine-3-carboxylic acid

Using essentially the procedure of Example 75, Step 8, the desired product, m.p. 184°C (dec.), is prepared from benzyl N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-(3S)-pyrrolidine-3-carboxylate.

Example 78

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-(2S)-2-carboxymethylpyrrolidine

Step 1: N-CBZ-pyrrolidine-(2S)-2-carboxyl chloride

N-CBZ-L-proline (3.0g) is dissolved in methylene chloride (60 ml) and oxalyl chloride (1.25 ml) is added. The solution is cooled to 0°C and dimethylformamide (0.2 ml) is added dropwise. After stirring at 0°C for about 4 [illegible] and the product used, without further treatment for the next [illegible].

Step 2: benzyl 2-(N-CBZ-(2S)-pyrrolidin-2-yl)acetate

N-CBZ-pyrrolidine-(2S)-2-carboxyl chloride (crude product from the previous step) is dissolved in THF (25 ml) and acetonitrile (25 ml) and the solution cooled to 0°C. A solution of 2.0M trimethylsilyldiazomethane in hexanes (12.03 ml) is added and the mixture stirred for 5 hours at 0°C. The solution is concentrated in vacuo and the residue dissolved in a solution of 2,4,6-trimethylpyridine (8 ml) and benzyl alcohol (8 ml). This solution is heated at 180°C for 10 minutes, cooled, and diluted with benzene (200 ml). The benzene solution is washed with water, 1N HCl, 10% sodium carbonate solution, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash chromatography, eluting with a gradient of 20% to 30% ether in hexane, to give the desired product.

Step 3: 2-(N-BOC-(2S)-pyrrolidin-2-yl)acetic acid

Benzyl 2-(N-CBZ-(2S)-pyrrolidin-2-yl)acetate (2.31g) and di-t-butyl dicarbonate (1.78g) are dissolved together in methanol (30 ml) and 10% palladium on carbon (0.46g) is added and the mixture stirred under a hydrogen atmosphere for about 18 hours. The mixture is filtered, and concentrated in vacuo to give the desired product.

Step 4: benzyl 2-(N-BOC-(2S)-pyrrolidin-2-yl)acetate

Using essentially the procedure of Example 75, Step 1, and purifying the crude product by flash chromatography, eluting with a gradient of 5% to 10% ethyl acetate in hexane, the desired product is prepared from 2-(N-BOC-(2S)-pyrrolidin-2-yl)acetic acid.

Step 5: benzyl 2-((2S)-pyrrolidin-2-yl)acetate

Using essentially the procedure of Example 75, Step 2, the desired product is prepared, as the trifluoroacetate salt from benzyl 2-(N-BOC-(2S)-pyrrolidin-2-yl)acetate.

Step 6: benzyl 2-(N-(N-BOC-L-prolyl)-(2S)-pyrrolidin-2-yl)acetate

BOC-L-proline (0.712g) is dissolved in methylene chloride (18 ml), the solution cooled to -10°C, and triethylamine (0.46 ml) followed by BOP-Cl (0.843g) are added. The solution is stirred at -10°C for about 30 minutes and a solution of benzyl 2-((2S)-pyrrolidin-2-yl)acetate trifluoroacetate (2.76 mmol) is methylene chloride (5 ml) containing triethylamine (0.84 ml) is added. The solution is stirred at room temperature for about 18 hours, diluted with ethyl acetate (100 ml), and the organic solution washed with water, 1N HCl, 10% sodium carbonate solution, and brine. The organic solution is dried over magnesium sulfate, filtered and concentrated in vacuo. The residue is purified by flash chromatography, eluting with a gradient of 20% to 30% ethyl acetate in methylene chloride, to give the desired product.

Step 7: N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-(2S)-2-carboxymethylpyrrolidine

Using essentially the procedures of Example 77, Steps 9, 10, 11, 12, and 13, the desired product, m.p. 179-181°C, is prepared from benzyl 2-(N-(N-BOC-L-prolyl)-(2S)-pyrrolidin-2-yl)acetate.

Using appropriate starting materials and procedures analogous to those used in the previous examples, the following compounds are prepared.

Example 79

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-anthranilic acid

Example 80

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucylglycine, m.p. 133°C (dec.)

Example 81

[illegible]

Example 82

N-[(3R)-2-(3-chlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-β-alanine, m.p. 152°C (dec.)

Example 83

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-β-alanine, m.p. >210°C

Example 84

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-4-aminobutyric acid, m.p. 182°C (dec.)

Example 85

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-5-aminovaleric acid, m.p. 156°C (dec.)

Example 86

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-(1S)-(1-phenyl)-β-alanine, m.p. 169-171°C

Example 87

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-N-(2-methylpropyl)glycyl-β-alanine, m.p. 134-136°C

Example 88

N-[(3R)-2-(quinolin-3-ylcarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide, m.p. 211-215°C

Example 89

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-N-methyl-β-alanine

Example 90

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-N-methyl-β-alanine, m.p. 229°C (dec.)

Example 91

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-homoprolyl-β-alanine

Example 92

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-(2S)-2-(5-carboxypentyl)pyrrolidine, m.p. 130-132°C

Example 93

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-(1R)-(1-phenyl)-β-alanine, m.p. 200°C (dec.)

Example 94

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolylglycine, m.p. 189°C

Example 95

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-homoprolyl-L-aspartic acid amide, dicyclohexylammonium salt

Example 96

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-(1R)-(1-phenyl)-β-alanine, m.p. 183°C

Example 97

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-N-methyl-(1R)-(1-phenyl)-β-alanine, m.p. 172-174°C

Example 98

N-[(3R)-2-(naphth-2-ylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-(1R)-(1-phenyl)-β-alanine, m.p. 181-183°C

Example 99

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-L-phenylalanine, m.p. 174-176°C

Example 100

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-β-glutamic acid, m.p. 176-179°C

Example 101

N-[N-[(3R)-2-(naphthyl-2-carbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotic acid

Example 102

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-L-aspartic acid, m.p. 189-191°C

Example 103

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-trans-pyrrolidine-3,4-dicarboxylic acid

Example 104

N-[(3R)-2-(N-methyl-3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-β-alanine

Example 105

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-(3R)-pyrrolidine-3-carboxylic acid

Example 106

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-prolyl]-3-aminobenzoic acid

Example 107

N-[2-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonylamino]benzoyl]-β-alanine

Example 108

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-N-methyl-(1S)-(1-phenyl)-β-alanine

Example 109

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]iminodipropionic acid

Example 110

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-L-proline

Example 111

N-[(3R)-2-(adamantyl-2-carbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-β-alanine

Example 112

[N-[(3R)-2-(adamant-2-yloxycarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-β-alanine

Example 113

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-L-(N-methyl)aspartic acid

Example 114

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-L-(N-ethyl)aspartic acid

The effectiveness of the compounds of this invention as gastrin or cholecystokinin antagonists may be determined by the following

pharmacologic tests which evaluate the gastrin and cholecystokinin antagonist activity of said compounds. The CCK-A Receptor Binding Assay, CCK-B Receptor Binding Assay and the Gastrin Receptor Binding Assay are standard test procedures. The CCK-A Receptor Binding Assay is essentially that of Chang, et al., "Characterization of the Binding of [^{3}H]-(±)-L-364,718: A New Potent, Nonpeptide Cholecystokinin Antagonist Radioligand Selective for Peripheral Receptors", *Molecular Pharmacology*, **30**: 212-217 (1986). The CCK-B Receptor Binding Assay is based on that of Chang, et al., "Biochemical and pharmacological characterization of an extremely potent and selective nonpeptide cholecystokinin antagonist", *Proc. Natl. Acad. Sci. USA*, **83**, 4923-4926 (1986). The Gastrin Receptor Binding Assay is essentially that of Chang, et al., "Characterization of [^{3}H] Pentagastrin Binding in Guinea Pig Gastric Glands - An Alternative Convenient Ligand for Receptor Binding Assay", *Biochemical and Biophysical Research Communications*, **134** (2): 895-899 (1986).

CCK-A Receptor Binding Assay

Materials

Wash Buffer (for use with Brandel Cell Harvester):

30 liters (L) of 50 mM Tris, pH 7.7: Dissolve 181.7g Tris base in 4 L deionized water at room temperature. Adjust pH to 7.7 with 6N HCl and Q.S. to 30 L.

Assay Buffer:

50 mM Tris-Cl, 5 mM $MgCl_2$, 5 mM dithiothreitol, 0.14 mg/ml bacitracin, and 2 mg/ml bovine serum albumin (BSA).

1 liter of 5X stock buffer:

30.28g Tris base per 800 ml deionized water, 5.08g $MgCl_2 \cdot 6H_20$, pH to 7.7 at room temperature with 6N HCl and Q.S. to 1 liter, store at 4°C.

250 ml working buffer (kept on ice):

50 ml of 5X stock buffer 0.1928g dithiothreitol (5 mM), 35 mg bacitracin (0.14 mg/ml), and 0.5g BSA (2mg/ml).

Unlabeled L-364,718 (nonpeptide ligand):

Unlabeled L-364,718 (N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-1H-indole-2-carboxamide) (300 nM final concentration) is used to define nonspecific binding. A 3 mM solution is made in absolute

Receptors Preparation:

A Sprague-Dawley rat is sacrificed by asphyxiation with carbon dioxide and the pancreas removed. The tissue is immersed in cold wash buffer and carefully trimmed of fat, connective tissue, blood vessels, blotted and weighed. The tissue is homogenized in a Sorvall SS-34 centrifuge tube in 50 volumes of wash buffer using a Polytron at setting 7 for 15 seconds. The tissue is centrifuged (Sorvall SS-34) at 19,000 rpm for 10 min. The supernatant is poured off and the pellet resuspended in sufficient buffer to obtain a concentration of 40 mg tissue wet weight/ml. Separate aliquots (2.3ml) are placed in each of 8 centrifuge tubes and centrifuged as before. The supernatants are poured off and the pellets stored at -70°C. Stored pellets are sufficient for the assay of 160 tubes and are stable for 1-2 months.

During the assay the stored membranes are resuspended in 40 ml of assay buffer by scraping the pellet off the wall of the centrifuge tube and washing it into a teflon-glass homogenizer. Membranes are resuspended by 5 passes with the teflon pestle and the membranes stored on ice until ready for use.

Preparation of Compounds:

Compounds of the present invention to be tested are prepared in DMSO (dimethyl sulfoxide) or in assay buffer. The majority of compounds of the present invention active as CCK antagonists generally require DMSO for

complete solubility. Approximately 2-3 mg of compound is weighed directly into a 13 x 100 mm test tube and sufficient DMSO added to obtain a working stock solution at a concentration 100 fold greater than the highest concentration being tested in the assay. A total of 10 µl of each concentration of drug is added into a final volume of 1 ml to yield a 100 fold dilution of the working stock solution. Control binding tubes ("totals and nonspecifics") are also treated with 10 µl DMSO.

Radioligand Preparation:

^{3}H-L-364,718 is obtained from New England Nuclear (Cat. # 971) and is used as supplied. The final assay concentration of ^{3}H-L-364,718 in assay buffer should be 0.2 nM in a final assay volume of 1 ml. ^{3}H-L-364,718 (0.2 pmol) is added into the assay in a volume of 25 µl (8 nM working stock solution). The required dilution (usually > 1000 fold) is obtained by dividing the working stock concentration into the concentration of the specific lot of ^{3}H-L-364,718.

Assay Procedure

Samples are prepared in triplicate and a "total" (buffer addition) and "nonspecific" (300 nM unlabeled L-364,718) set of tubes included in each set of 24 tubes. The "total" assay tubes contain 25 µl ^{3}H-L-364,718 solution, 250 µl membrane suspension, 10 µl DMSO and 715 µl assay buffer. The "nonspecific" assay tubes contain 25 µl ^{3}H-L-364,718 solution, 10 µl unlabeled L-364,718 solution, 250 µl membrane suspension, 10 µl DMSO, and 705 µl assay buffer. The remaining 6 sets of triplicates are used either for screening or IC_{50} determinations. These tubes contain 25 µl ^{3}H-L-364,718 solution, 250 µl membrane suspension, 10 µl of a solution of the compound of the present invention to be tested, and 715 µl assay buffer. The order of addition is compound of the present invention-DMSO, buffer, unlabeled L-364,718, ^{3}H-L-364,718, and, to start the assay, membrane suspension.

While tubes are incubating in a shaking water bath at 37°C for 30 minutes, Brandel deposit/dispense filters are presoaked in wash buffer. Following the end of the incubation, sets of 24 tubes are rapidly washed with assay buffer as follows. Assay buffer is added to the incubation tubes to the

height of the uppermost cross support in the standard Brandel test tube rack and the contents immediately aspirated. This process is repeated twice more, the filter removed, marked and the next set of 24 tubes processed. It is critical that the filtration-washing step be completed as quickly as possible; preferably within 20 seconds. The individual filter rings from a single filter strip are dispensed into 7 ml minivials and 5 ml of scintillation cocktail (AquaSol 2, Dupont) added using the Brandel deposit/dispenser apparatus. Samples are counted following either 30 minutes of low speed shaking on a horizontal shaker (Eberbach Corp.) or a prolonged equilibration period (> 2 hr) in the scintillation counter (Beckman model 6000IC).

For screening studies, or in the determination of IC50s, data are expressed as the degree of inhibition of specific binding by the addition of a compound of the present invention. Specific binding is defined as the difference between the counts from "total" and "nonspecific" tubes. The nonspecific binding value is also subtracted from each sample and the specific binding expressed as a percentage of that seen in the absence of a compound of the present invention. For screening (usually at 100 µM) the percent of specific binding is the desired quantity, whereas for determination of the IC_{50} concentration, one tests multiple concentrations of compounds of the present invention to define the concentration at which specific binding is reduced 50%.

CCK-B Receptor Binding Assay

Materials

Wash Buffer:

Tris base (181.7g) is dissolved in Millipore deionized water (4 L) and the pH adjusted to 7.4 with 6N HCl, then diluted to 30 L. Prior to use pH neutralized bovine serum albumin (1.0 g/L) is added.

Homogenization Buffer:

One liter 5X (i.e. five-fold concentrated) stock: Tris base (30.28g) is dissolved in Millipore deionized water (900 ml) and the pH adjusted to 7.7 with

6N HCl, then diluted to 1 L. For use, 40 ml of 5X stock is diluted with 160 ml of Millipore deionized water.

Assay Buffer:

5X stock solution: Hepes (11.92g), $MgCl_2$, EGTA (380.4 mg) and NaCl (37.99g) are dissolved in 900 ml Millipore deionized water and the pH is adjusted to 6.5 with NaOH, then diluted to 1 L. For use 30 ml of 5X stock solution is diluted with 120 ml water and 37.5 mg bacitracin is added.

Preparation of Receptors:

A male Hartley guinea pig weighing 250-300g is sacrificed by asphyxiation with carbon dioxide and decapitated. The brain is removed to an ice-cold surface, rinsed with physiological saline and the cerebral cortex grossly dissected. The dissected tissue is blotted, weighed, and homogenized in 50 volumes of homogenization buffer in a 150 ml beaker using a Polytron at setting 5 for 10 seconds. The homogenate is centrifuged at 19,000 rpm in a Sorvall SS-34 centrifuge for 10 minutes, and the pellets rinsed into a beaker and homogenization in 50 volumes of homogenization buffer is repeated. 12.5 ml of homogenate (i.e. 250 mg wet weight) is aliquotted to each of several centrifuge tubes and centrifuged at 19,000 rpm for 10 minutes. The supernatant is poured off and the tubes stored, covered, at -70°C. For use, the pellet is thawed, and suspended in assay buffer sufficient to give 10 mg tissue wet weight/ml.

Preparation of Compounds to be Tested:

Compounds of the present invention or standards are freshly prepared for each assay in DMSO or assay buffer (if the compound to be tested is soluble in the assay buffer). 2-3 mg of compound is dissolved in sufficient assay buffer to give a concentration 10-fold that of the desired concentration in the assay or is dissolved in sufficient DMSO to give a concentration 1000-fold that of the desired concentration in the assay. A series of 3- and 3.33-fold dilutions are prepared in assay buffer such that a 50µl aliquot gives the desired concentration in the assay. Control tubes ("totals" and "nonspecifics) are

treated with the same concentration of DMSO which has been to added to compound tubes.

Preparation of Unlabeled CCK_8:

Unlabeled CCK_8 (obtained from Research Plus, Inc.) is used to define nonspecific binding. A 200 µM stock is prepared in Millipore deionized water and stored as 100 µL aliquots at -70°C. With an assay volume of 500 µL, dilution of the stock tubes with 900 µL of assay buffer, and addition of 25 µL of this to each "nonspecific" assay tube will yield a final concentration of 1 µM.

^{125}I-Bolton Hunter-CCK_8 (obtained from New England Nuclear) is diluted in sufficient assay buffer to obtain a final concentration of 40 pM in assay (approximately 55-57,000 cpm/25µL).

Assay Procedure

Samples are prepared in triplicate and a "total" (buffer addition) and "nonspecific" (CCK_8) set of tubes included in each set of 24 tubes. The "total" assay tubes contain 375 µL of assay buffer, 25 µL of ^{125}I-CCK_8 solution, and 100µL of receptor suspension. The "nonspecific" tubes contain 25 µL of cold CCK_8 solution, 350 µL of assay buffer, 25µL of ^{125}I-CCK_8 solution, and 100µL of receptor suspension. The remaining tubes are triplicates of each of 6 concentrations of the compound of the present invention or standard to be tested. These contain 50 µL of compound solution, 325 µL of assay buffer, 25µL of ^{125}I-CCK_8 solution, and 100µL of receptor suspension. The order of addition of assay components is buffer, DMSO (if necessary), compound to be tested, unlabeled CCK_8, radioligand, and, finally, membrane suspension.

The tubes are incubated at 37°C in a shaking water bath for 30 minutes. During incubation Brandel filters are presoaked in wash buffer. When incubation is complete, each of 24 tubes is rapidly washed 3 times using a Brandel Cell Harvester. Wash buffer is added to the 15 x 100 Minisorp assay tubes to a height just above the lower cross support in the standard Brandel test tube rack (about 4 mL) and the contents immediately aspirated. This step

is repeated twice more. After the third wash, the filter is removed and the 24 circles are punched out, placed in 12 x 75 NUNC polypropylene tubes and counted in a gamma counter for 1 minute.

For screening studies, or in the determination of IC_{50} values, results are expressed as the degree of inhibition of specific binding by the addition of compound of the present invention. Specific binding is defined as the difference between the counts from "total" and "nonspecific" tubes. The nonspecific binding value is also subtracted from each sample and the specific binding expressed as a percentage of that seen in the absence of a compound of the present invention. For screening the percent of specific binding is the desired quantity, whereas for determination of the IC_{50} concentration, one tests multiple concentrations of compounds of the present invention to define the concentration at which specific binding is reduced 50%.

Gastrin Receptor Binding Assay

Preparation of Glands

Solutions:

Phosphate Buffered Saline (PBS): 8.743g NaCl, 523 mg K_2HPO_4 and 76.8 mg NaH_2PO_4 is dissolved in 900 ml of deionized water, the pH of the solution is adjusted to 7.3 with 5N NaOH, then Q.S. to 1 L.

Buffer A: Powdered Basal Medium Eagle (BME) containing Earle's Salts, L-glutamine and 25 mM HEPES without bicarbonate (Sigma Cat. number B 4391) sufficient to make 3 liters is stirred into 2.7 L of deionized water, 6.6 mg sodium bicarbonate is added and the mixture stirred to give dissolution. The solution is then equilibrated with 95% O_2/5% CO_2 gas followed by titration to a pH of 7.4 with NaOH, then Q.S. to 3 L.

Buffer B: 18.75 mg of collagenase A and 25 mg of pH neutralized BSA is dissolved in 25 ml of Buffer A.

Buffer C: 0.3g of BSA is dissolved in 300 ml of Buffer A.

Buffer D: 6.25 mg Bacitracin is dissolved in 25 ml of Buffer A.

Method:

A guinea pig (Hartley Strain) weighing 150-200 grams, is sacrificed by CO_2 asphyxiation and the stomach immediately excised, cut along the greater curvature, cleaned out and immediately immersed in a beaker containing cold PBS, pH 7.3, to insure thorough cleaning. The fundic mucosa is gently scraped off the submucosa and added to a preweighed 50 ml plastic centrifuge tube containing 30 ml of cold Buffer A. The weight of the plastic centrifuge tube weight of the mucosa thus determined is recorded for later calculations. The mucosa is then washed twice in Buffer A. After the final wash, the tissue is minced and is placed in a 100-ml glass beaker containing about 1.0 ml of Buffer A, and washed twice again by repeated centrifugation at 50Xg for 5 minutes each and aspiration of supernatant. The washed tissue fragments are then added to a glass Erlenmeyer flask containing 25 ml of Buffer B and incubated in a Dubnoff shaking water bath at 37°C for 30 minutes in a 95% O_2/5% CO_2 atmosphere. After the incubation, the digested tissue fragments in the Collegenase-buffer solution are triturated, filtered through a 200-micron nylon mesh and centrifuged at 50Xg for 5 minutes. The supernatant is aspirated and discarded, the tissue washed 2X in Buffer C, resuspended in same buffer, incubated in a 37°C water bath in an atmosphere of 95% O_2/5% CO_2 for 5 minutes, and centrifuged. The pelleted glands are suspended in Buffer D at a desired concentration of $2x10^5$ glands/ml to use in the receptor binding assay.

Assay Method

Assay Buffer: Buffer A as above

Ligand Solutions:

^{125}I-(Leu-15)-Gastrin: 100 microcurie dissolved in 2.0 ml of Buffer A to make 50 microcurie/ml; stored in 50 µl aliquots under Argon at -70°C.

^{125}I-(15-methionine)-Human Gastrin: 50 microcurie/ml in deionized water, stored in 50 µl aliquots as above.

(Leu 15)-Gastrin 17: 5.2 mg of (Leu-15)- Gastrin is dissolved in 10 ml of Buffer A and stored in 30 µl aliquots. At the time of assay a 1:10 dilution is made and 10 µl/assay tube is used.

Method:

Six minisorp tubes (16x100 mm) are serially marked and divided into two groups thus: tubes #1, #2, and #3 are marked "T" for "Totals" and tubes #4, #5, and #6 are marked "NS" for "Non-Specifics." Into each of the six tubes are added 220µl of prepared glands in Buffer D; 20 µl of Buffer A in tubes #1, #2, and #3; 10 µl, in tubes #4, #5 and #6; (10 µl of (Leu-15)-Gastrin (25 µM) in tubes #4, #5, and #6. The six tubes are then transferred immediately to a 25°C water bath and challenged each with 10 µl ^{125}I-(Leu-15)-Gastrin diluted as per calculation. The tubes are then covered with a gas hood connected to a 95% 0_2/5% CO_2 gas source and mechanically agitated in a shaker for 30 minutes.

At the end of the incubation period, the assay mixtures are each filtered through a Whatman glass fiber filter B on a Brandel tissue harvester and washed twice with Buffer A. The filters are pre-soaked in Buffer C before use. The filter strips are removed after the final wash and individual filters counted in a Gamma Counter. The counts from the "Non-Specific" tubes are then averaged and subtracted from the average "Totals" to give the Specific Counts.

For screening compounds, the above assay method is utilized except that triplicate tubes are prepared for each concentration of compound of the present invention to be assayed. 20 µl of a solution of each compound to be assayed in triplicate are added to each designated tube.

In displacement studies the IC_{50} value is the concentration of compound causing a 50% decrease in specific binding of a tracer amount of ^{125}I-(Leu-15) Gastrin. The IC_{50} value is derived from a plot of the log of the displacer concentration against the percentage of specific binding.

Compounds of the present invention exhibit marked activity in the foregoing tests and are considered useful for treatment or prevention of cholecystokinin and gastrin related disorders. Results of testing of compounds of the present invention by the above methods are presented in the table below.

In Vitro Binding Data

Compound of Example	IC_{50} (μM) CCK-A	CCK-B	Gastrin
1	>300		12
2	>300		60
3	>300		>300
4	>300		>300
5	50-60		59
6	62		60
7	25		-
8	82		78
9	230		25
10	25		15
11	34		3.0
12	170		29
13	10		>300
14	>100		5.5
15	9		10
16	10-25		>300
17	>10		100
18	25		55
19	20		8
20	>30		80
21	-		90
22	>10		>300
23	>10		>300
24	36		.77
25	-		.23
26	100		1.3
27	14		.41
28	9		.91
38	68		16.7
39	>100		.23
40	41		6
41	4.0		10.0
42	37		30

In Vitro Binding Data

(Cont'd)

Compound of Example	IC_{50} (μM) CCK-A	CCK-B	Gastrin
43	98		2.2
44	78		32
45	3.9		2.6
48	35		1.7
49	92		12
50	100		17
53	>100		6.8
54	48.0		3.3
55	34		>30
56	100		22
57	65		18
58	34.0		2.0
59	65		15
60	>100		6.4
61	9.3		1.2
62	86		4.1
63	29.0		5.3
64	>100		7.3
65	24		0.54
66	100		2.0
70	-		4.0
74	16.1		0.03
75	10	0.111	0.026
76	11.7	0.679	0.230
77		0.228	0.0409
78			0.0585
79	1.15	0.0381	0.0323
80	14.9		1.6
81	29	0.0978	0.025
82	34	1.48	0.380
83	20		0.540

In Vitro Binding Data

(Cont'd)

Compound of Example	IC_{50} (μM) CCK-A	CCK-B	Gastrin
84	8	0.229	0.174
85	9.9	0.306	0.154
86	4.6	0.59	0.081
87	7	1.34	0.523
88	43.2		71.0
89	19.9		0.200
90			>1
91	10		5.4
92	23.7	0.543	0.610
93			0.309
94			0.0745
95			0.66
96		0.346	0.231
97			0.358
98			0.197
99			0.207
100			0.0516
102			0.0157

The compounds of the present invention are useful for treatment or prevention of cholecystokinin and gastrin related disorders of the central nervous, gastrointestinal, and appetite regulatory systems. It is believed that the compounds exhibit such utility by virtue of their ability to antagonize the actions of cholecystokinin and gastrin.

The compounds of the present invention may be administered to a patient in need of such treatment or prevention either alone or in combination with a pharmaceutically acceptable carrier. The compounds may be administered orally or parenterally including intramuscularly, intravenously, intraperitoneally, subcutaneously and topically.

The compounds of this invention may be formulated for administration in any convenient way, and the invention includes within its scope

pharmaceutical compositions containing at least one compound according to the invention adapted for use in human or veterinary medicine. Such compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients. Suitable carriers include diluents or fillers, sterile aqueous media and various non-toxic organic solvents. The compositions may be formulated in the form of tablets, capsules, lozenges, troches, hard candies, powders, aqueous suspensions, or solutions, injectable solutions, elixirs, syrups and the like and may contain one or more agents selected from the group including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a pharmaceutically

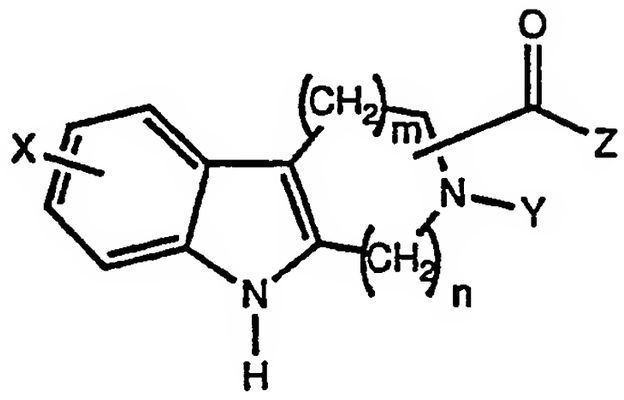
The particular carrier and the ratio of gastrin and cholecystokinin antagonist compound to carrier are determined by the solubility and chemical properties of the compounds, the particular mode of administration and standard pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate and dicalcium phosphate and various disintegrants such as starch, alginic acid and certain complex silicates, together with lubricating agents such as magnesium stearate, sodium lauryl sulphate and talc, can be used in producing tablets. For a capsule form, lactose and high molecular weight polyethylene glycols are among the preferred pharmaceutically acceptable carriers. Where aqueous suspensions for oral use are formulated, the carrier can be emulsifying or suspending agents. Diluents such as ethanol, propylene glycol, glycerin and chloroform and their combinations can be employed as well as other materials.

For parenteral administration, solutions or suspensions of these compounds in sesame or peanut oil or aqueous propylene glycol solutions, as well as sterile aqueous solutions of the soluble pharmaceutically acceptable salts described herein can be employed. Solutions of the salts of these compounds are especially suited for intramuscular and subcutaneous injection purposes. The aqueous solutions, including those of the salts dissolved in pure distilled water, are also useful for intravenous injection purposes, provided that their pH is properly adjusted, they are suitably buffered, they are made isotonic with sufficient saline or glucose and sterilized by heating or microfiltration.

The dosage regimen in carrying out the method of this invention is that which insures maximum therapeutic response until improvement is obtained and thereafter the minimum effective level which gives relief. In general, the oral dose may be between about 10 mg/kg and about 300 mg/kg, and the i.v. dose about 0.1 mg/kg to about 200 mg/kg, bearing in mind, of course, that in selecting the appropriate dosage in any specific case, consideration must be given to the patient's weight, general health, age, and other factors which may influence response to the drug. The drug may be administered orally 1 to 4 times per day, preferably twice daily.

WHAT IS CLAIMED IS:

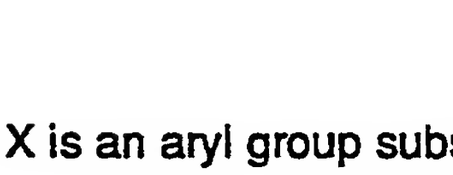
1. A compound of the formula

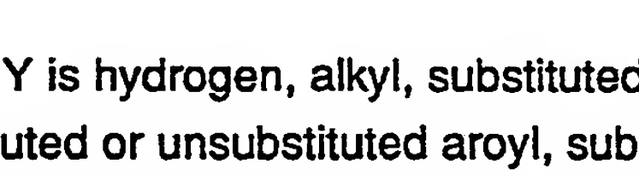


X is an aryl group substituent;

Y is hydrogen, alkyl, substituted or unsubstituted aralkyl, acyl, substituted or unsubstituted aroyl, substituted or unsubstituted heterocyclylcarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl where the alkyl groups may be the same or different, substituted or unsubstituted arylcarbamoyl, substituted or unsubstituted N-alkyl arylcarbamoyl, alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, or substituted or unsubstituted aralkoxycarbonyl;

Z is substituted or unsubstituted nitrogen-containing heterocyclyl, $-NR_aR_b$ where R_a and R_b are independently hydrogen, alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted diarylalkyl, or, when taken together, R_a and R_b may form $-(CH_2)_t-$ where t is 3, 4, or 5, or Z is



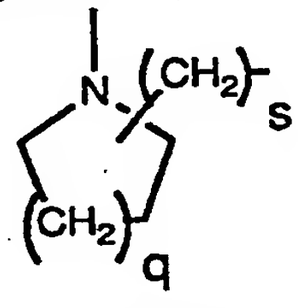


where

A_1 and A_2 are independently alkylene, substituted or unsubstituted phenylene, cycloalkylene, arylalkylene, arylalkylalkylene, alkoxycarbonylalkylalkylene, aryloxycarbonylalkylalkylene,

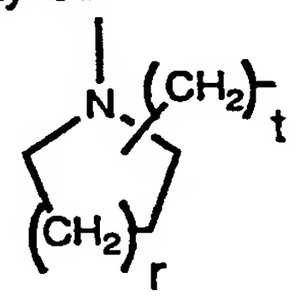
aralkoxycarbonylalkylalkylene, carboxyalkylalkylene, carbamoylalkylalkylene, alkylthioalkylalkylene, hydroxymethylmethylene, alkoxyalkylalkylene, aralkoxyalkylalkylene, aralkoxyalkylene, (1-hydroxyethyl)methylene, (4-hydroxyphenyl)methylmethylene, indol-3-ylmethylmethylene, imidazol-4-ylmethylmethylene, guanidinoalkylalkylene, or aminoalkylalkylene,

$-NR_c-A_1-$ may be



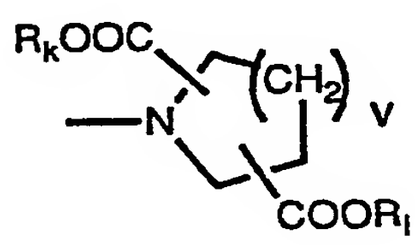
where q is 0, 1, 2, or 3, and
s is 0, 1, or 2; and

$-NR_d-A_2-$ may be



where r is 0, 1, 2, or 3, and
t is 0, 1, or 2;

B is hydroxy, alkoxy, substituted or unsubstituted aralkoxy, substituted or unsubstituted aryloxy or $-NR_fR_g$ where R_f and R_g are independently hydrogen, alkyl, substituted or unsubstituted aralkyl, carboxyalkyl, alkoxycarbonylalkyl, substituted or unsubstituted aryloxycarbonylalkyl or substituted or unsubstituted aralkoxycarbonylalkyl, or, when taken together, R_f and R_g may form $-(CH_2)_u-$ where u is 3, 4, or 5, or B is



where R_k and R_l are independently hydrogen, alkyl, or substituted or unsubstituted aralkyl,
and v is 0, 1, or 2;

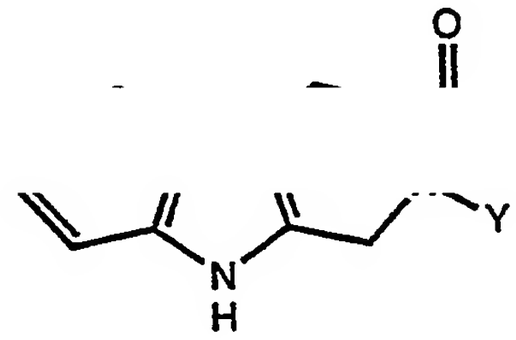
R_c and R_d are independently hydrogen, alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted aralkyl;

m is 0, 1, 2, or 3; and

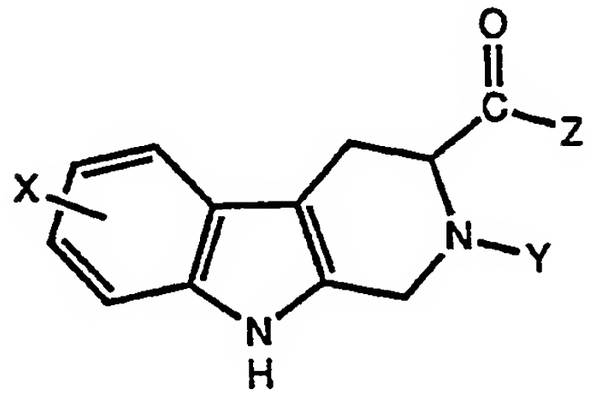
n is 0, 1, 2, 3, or 4;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1 of the formula

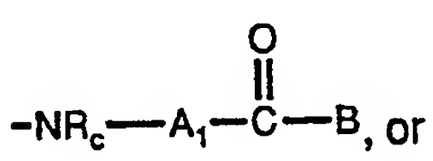


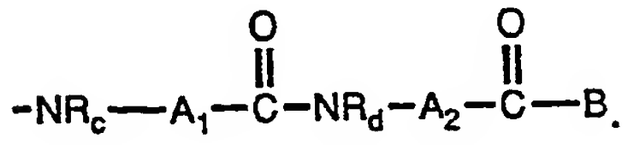
3. A compound of claim 2 of the formula



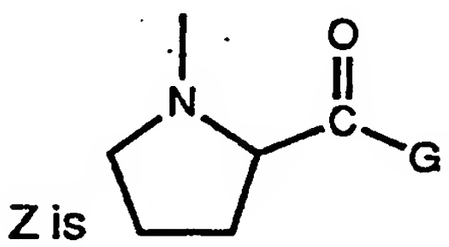
4. A compound of claim 3 wherein:

Z is $-NR_aR_b$,

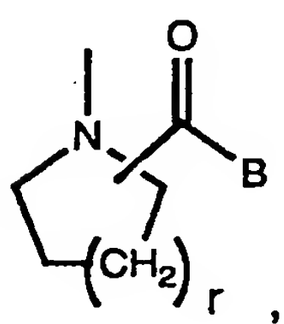




5. A compound of claim 4 wherein:

Z is 

where G is



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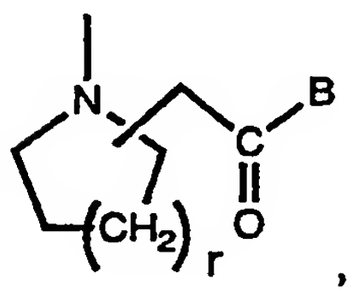

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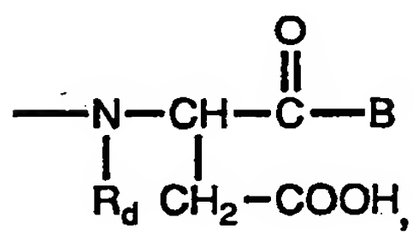

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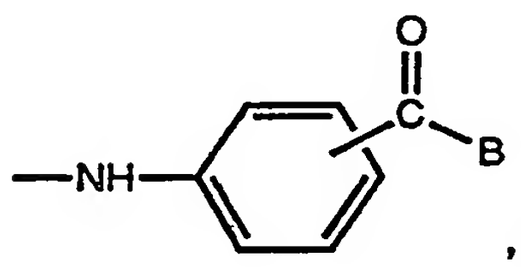
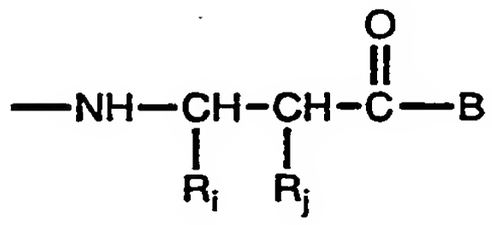


, or



where

B is hydroxy, alkoxy, aralkoxy, aryloxy or $-NR_fR_g$ where R_f and R_g are independently hydrogen, alkyl, or aralkyl; and

R_i and R_j are independently hydrogen, or alkyl.

6. A compound or claim 4 wherein:

Y is substituted or unsubstituted aroyl, alkylcarbamoyl, substituted or unsubstituted arylcarbamoyl, substituted or unsubstituted N-alkyl arylcarbamoyl, alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, or substituted or unsubstituted aralkoxycarbonyl.

7. A compound of claim 6 wherein:

unsubstituted arylcarbamoyl, or substituted or unsubstituted aryloxycarbonyl.

8. A compound of claim 7 wherein:

Y is substituted or unsubstituted arylcarbamoyl.

9. A compound of claim 1 which is

N-[(3R)-1,2,3,4-Tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide;

N-[(3S)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide;

N-[(3R)-1,2,3,4-Tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-aspartic acid amide;

N-[(3S)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-aspartic acid amide;

(3R)-3-(2,2-Diphenyl)ethylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole;

(3R)-3-Diphenylmethylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole; or

N-[(3R)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide-ß-benzyl ester;

or a pharmaceutically acceptable salt thereof.

10. A compound of claim 1 which is

N-[(3R)-2-benzoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]-indole-3-carbonyl]-L-aspartic acid amide ß-benzyl ester;

N-[(3R)-2-benzoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]-indole-3-carbonyl]-L-aspartic acid amide;

N-[(3R)-2-benzoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide;

N-[(3R)-2-(2-naphthoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide;

(3R)-2-(2-naphthoyl)-3-(2-pyrrolidin-1-ylcarbonyl)phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole;

N-[(3R)-2-(1-naphthoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide-ß-benzyl ester;

N-[(3R)-2-(2-naphthoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide-ß-benzyl ester;

N-[(3R)-2-(3-methylbenzoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide; or

N-[(3R)-2-(3,4-dichlorobenzoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide;

or a pharmaceutically acceptable salt thereof.

11. A compound of claim 1 which is N-[(3R)-2-(quinolin-3-ylcarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide or a pharmaceutically acceptable salt thereof.

12. A compound of claim 1 which is

N-(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-isoleucyl-L-aspartic acid amide;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetra-hydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-leucyl-D-aspartic acid amide;

N-[(3S)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetra-hydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-leucyl-D-aspartic acid amide;

N-[(3R)-2-(2,3-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-L-aspartic acid amide;

N-[(3R)-2-(4-chlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-asartic acid amide;

N-[(3R)-2-(3,5-dichlorophenylcarbamoyl)-1,2,3,4-tetra-hydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide; or

N-[(3R)-2-(3-fluorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide;

or a pharmaceutically acceptable salt thereof.

13. A compound of claim 1 which is

N-[(3R)-2-(3-Methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide;

N-[(3S)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide;

(3R)-3-(N,N-Dipentylcarbamoyl)-2-(3-methylphenyl-carbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole;

N-[(3R)-2-(3-methylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-isoleucyl-L-aspartic acid amide;

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-D-aspartic acid amide;

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-leucyl-D-aspartic acid amide;

N-[(3S)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-leucyl-D-aspartic acid amide;

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-D-aspartic acid amide;

N-[(3S)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-leucyl-L-aspartic acid amide;

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-leucyl-L-aspartic acid amide; or

N-[(3R)-2-(3,5-dimethylphenylcarbamoyl)-1,2,3,4-tetra-hydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide;

or a pharmaceutically acceptable salt thereof.

14. A compound of claim 1 which is

N-[(3R)-2-Phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide;

N-[(3R)-2-(2-naphthylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide;

N-[(3R)-2-(1-naphthylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide;

N-[(3R)-2-(4-methoxyphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-L-aspartic acid amide;

N-[(3R)-2-(3-methoxyphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide; or

N-[(3R)-2-(3-trifluoromethylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-

or a pharmaceutically acceptable salt thereof.

15. A compound of claim 1 which is

ethyl 4-N-[(3R)-2-carbobenzoxy-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]aminobenzoate;

ethyl 3-N-[(3R)-2-carbobenzoxy-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]aminobenzoate;

ethyl 2-N-[(3R)-2-carbobenzoxy-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]aminobenzoate;

(3R)-2-carbobenzoxy-3-(2-pyrrolidin-1-ylcarbonyl)phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole;

(3S)-2-carbobenzoxy-3-(2-pyrrolidin-1-ylcarbonyl)phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole;

2-[N-[(3R)-2-carbobenzoxy-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]]amino-N,N-dibutylbenzamide; or

ethyl 2-N-[(3S)-2-carbobenzoxy-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]aminobenzoate;

or a pharmaceutically acceptable salt thereof.

16. A compound of claim 1 which is

(3R)-2-(4-methoxy)phenylcarbamoyl-3-(2-pyrrolidin-1-ylcarbonyl)phenylcarbamoyl-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-1'amino-1'cyclopentyl-carbonyl-L-aspartic acid amide;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucinecyclohexylamide;

ethyl 4-N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]aminobenzoate;

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-aspartic acid dipentyl amide;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-homoprolyl-β-alanine;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-(2S)-2-(5-carboxypentyl)pyrrolidine;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-(1R)-(1-phenyl)-β-alanine;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-homoprolyl-L-aspartic acid amide; or

N-[2-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonylamino]benzoyl]-β-alanine;

or a pharmaceutically acceptable salt thereof.

17. A compound of claim 1 which is

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-ß-alanine;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-glycinamide;

N-[(3R)-2-(3-methylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-L-O-benzyl-serine;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-glycinamide;

N-[(3R)-2-(2,3-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-ß-alanine;

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-glycinamide;

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-leucyl-ß-alanine;

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucinamide;

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-phenylalanine amide;

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-asparagine;

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyido[3,4-b]indole-3-carbonyl]glycyl-L-aspartic acid amide;

N-[(3R)-2-(3-methylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-alanyl-L-aspartic acid amide;

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-O-benzyl-L-seryl-L-aspartic acid amide;

N-[(3S)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-leucyl-D-glutamic acid amide;

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-glutamic acid amide;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetra-hydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-glutamic acid amide;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucylglycine; or

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-β-alanine;

or a pharmaceutically acceptable salt thereof.

18. A compound of claim 1 which is

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indol-3-yl]carbonyl-L-prolyl-L-aspartic acid amide;

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-L-aspartic acid amide;

N-[(3S)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-prolyl-D-aspartic acid amide;

N-[(3S)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetra-hydro-9H-pyrido[3,4-b]indole-3-carbonyl]-D-prolyl-D-aspartic acid amide;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-β-alanine;

N-[(3R)-2-(3-chlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-β-alanine;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolylglycine;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-β-glutamic acid;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-L-aspartic acid;

N-[(3R)-2-(N-methyl-3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-β-alanine; or

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-L-proline;

or a pharmaceutically acceptable salt thereof.

19. A compound of claim 1 which is

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotic acid;

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-(3S)-pyrrolidine-3-carboxylic acid;

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-(2S)-2-carboxymethylpyrrolidine;

N-[N-[(3R)-2-(naphthyl-2-carbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotic acid;

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-trans-pyrrolidine-3,4-dicarboxylic acid; or

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-(3R)-pyrrolidine-3-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

20. A compound of claim 1 which is

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-anthranilic acid;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-(1S)-(1-phenyl)-β-alanine;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-(1R)-(1-phenyl)-β-alanine;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-N-methyl-(1R)-(1-phenyl)-β-alanine;

N-[(3R)-2-(naphth-2-ylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-(1R)-(1-phenyl)-β-alanine;

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-prolyl]-3-aminobenzoic acid; or

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-N-methyl-(1S)-(1-phenyl)-β-alanine;

or a pharmaceutically acceptable salt thereof.

21. A compound of claim 1 which is

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-N-methyl-L-aspartic acid amide;

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-4-aminobutyric acid;

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-N-methyl-β-alanine;

N-[N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]iminodipropionic acid;

N-[(3R)-2-(adamantyl-2-carbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-β-alanine;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-L-(N-methyl)aspartic acid; or

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-L-(N-ethyl)aspartic acid;

or a pharmaceutically acceptable salt thereof.

22. A compound of claim 1 which is

N-[N-[(3R)-2-(3,4-dichlorophenoxycarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl]-nipecotic acid; or

[N-[(3R)-2-(adamant-2-yloxycarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-prolyl-β-alanine;

or a pharmaceutically acceptable salt thereof.

23. A compound of claim 1 which is

N-[(3R)-2-(3-methylphenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]N-methyl-L-leucyl-L-aspartic acid amide;

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-N-(2-methylpropyl)glycyl-β-alanine;

N-[(3R)-2-(quinolin-3-ylcarbonyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-L-leucyl-L-aspartic acid amide; or

N-[(3R)-2-(3,4-dichlorophenylcarbamoyl)-1,2,3,4-tetrahydro-9H-pyrido[3,4-b]indole-3-carbonyl]-N-methyl-β-alanine;

or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising a therapeutically effective amount for antagonism of the function of cholecystokinin or gastrin in a human or other animal of a compound according to claim 1 and a pharmaceutically acceptable carrier.

25. A method for the prevention or treatment of cholecystokinin or gastrin-related disorders comprising the administration to a human or other animal patient in need of such therapy of a therapeutically effective amount of a compound according to claim 1.

26. A method for the prevention or treatment of cholecystokinin or gastrin-related disorders comprising the administration to a human or other animal patient in need of such therapy of a therapeutically effective amount of a pharmaceutical composition according to claim 24.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/04236

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

US CL: 546/86,87; 514/292
IPC(5): C07D 471/02 ; A61K 31/44 C07D 471/04

II FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
US CL	546/86,87

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

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III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A,P	US, A, 5,006,273 (SCHWORKENBERG ET AL.) PUBLISHED 16 APRIL 1991	10,19

- Special categories of cited documents: [10]
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15 NOVEMBER 1991	27 NOV 1991
International Searching Authority	**Signature of Authorized Officer**
ISA/US	For ALAN L. ROTMAN NGUYEN NGOC-HO INTERNATIONAL DIVISION

Form PCT/ISA/210 (second sheet) (Rev.11-87)

DC 11-22-91

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 25&26 because they relate to subject matter [2] not required to be searched by this Authority, namely:

"Method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods" is not required to be searched. See rule 39.1 part IV and PCT Article 17(2)(a)(i) respectively.

2. ☒ Claim numbers 1-8 and 24 . because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [3], specifically: The depicted formula of claim I includes 45 possible heterocyclic nitrogen containing ring systems. The problem is exaccerbated by the plethora of possibilities for the terms (y+z) alone which include all possible essential amino acids in every conceivable sequence which reads on hundreds of millions of compounds so that no meaningful international search can be rendered.

3. ☐ Claim numbers _____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [4]

This International Searching Authority found multiple inventions in this international application as follows:

I. Compounds, namely, 1,2,3,4-tetrahydro-9H-pyrido-[3,4-b] indole-3-carbonyl-L-proLyl-L-proline and related compounds. Claim 18 in-part and claim 19.

SEE SUPPLEMENTAL SHEET

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.